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HISTORY OF MEDICINE

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The search for a better oral contraceptive.

Now ORTHO introduces an oral contraceptive with even lower progestin potency.

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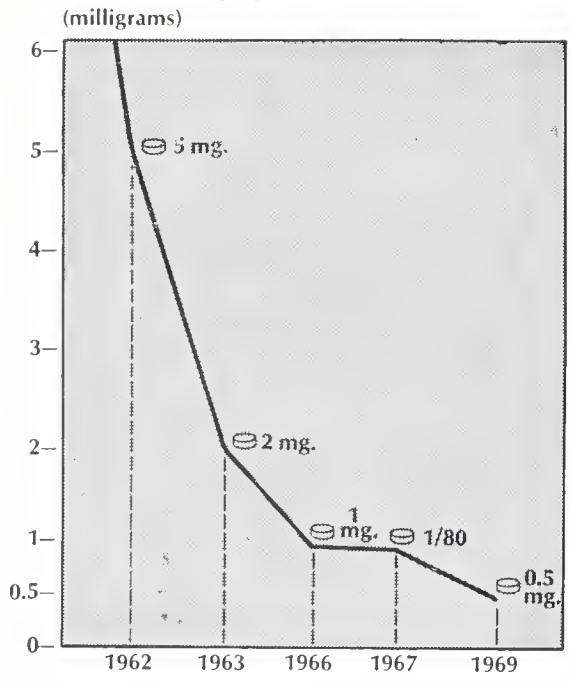

This chart shows how ORTHO has introduced new formulas for ORTHO-NOVUM tablets over the years. The aim has been to reduce progestational potency and find the best balance of estrogen in order to arrive at an oral contraceptive that is virtually 100% effective yet has minimum potency and good tolerance.*

Low-potency but effective

The uniquely balanced ORTHO-NOVUM 0.5 mg formula (0.5 mg norethindrone and 0.10 mg mestranol) has proved virtually 100% effective in recent clinical studies. Of 2,043 patients followed through 10,066 cycles, there were no pregnancies reported with regular use.

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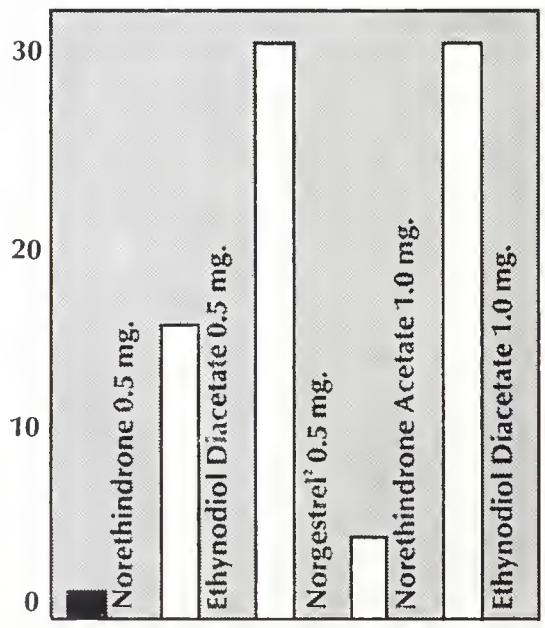
The progestin, norethindrone, is responsible for the low-potency level of ORTHO-NOVUM 0.5 mg. Of the progestins available, it is the one that provides truly low progestational potency on a daily basis with virtually 100% effectiveness. As a result, the potency-per-tablet of ORTHO-NOVUM 0.5 mg is considerably lower than that of any comparable tablet.



Comparative potency[1] of progestins in 0.5 and 1.0 mg oral contraceptives at daily dosage levels. Black bar represents norethindrone, the progestin contained in ORTHO-NOVUM 0.5 mg tablets.

Two easy-to-follow regimens

ORTHO-NOVUM 0.5 mg is available in two regimens: the 21-Day dosage in the "three weeks on, one week off" DIALPAK* Tablet Dispenser; and the 28-Day dosage in the strip dispenser. (It ensures that tablets are taken in the right order.) Both are easy to use. A few seconds is all it will take to explain either regimen to your patient.

Two regimens of ORTHO-NOVUM 0.5 mg: 21-Day DIALPAK Dispenser, and 28-Day in strip dispenser pak.

References

1. Greenblatt, R. B.; "Progestational Agents in clinical practice"; Medical Science; May 1967. (. . . it was imperative to establish, not by animal data but by human testing, the relative low potency of the various progestins. A test was devised, "the delay of menses test. . .")
2. Contains 0.25 mg *d*-norgestrel.

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Dosage and administration

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ORTHO-NOVUM 0.5 mg should not be taken: In the presence of malignant tumors of the breast or genital tract. In the presence of significant liver dysfunction or disease. In the presence of cardiac or renal disorders which might be adversely affected by some degree of fluid retention. During the period a mother is breast-feeding an infant.

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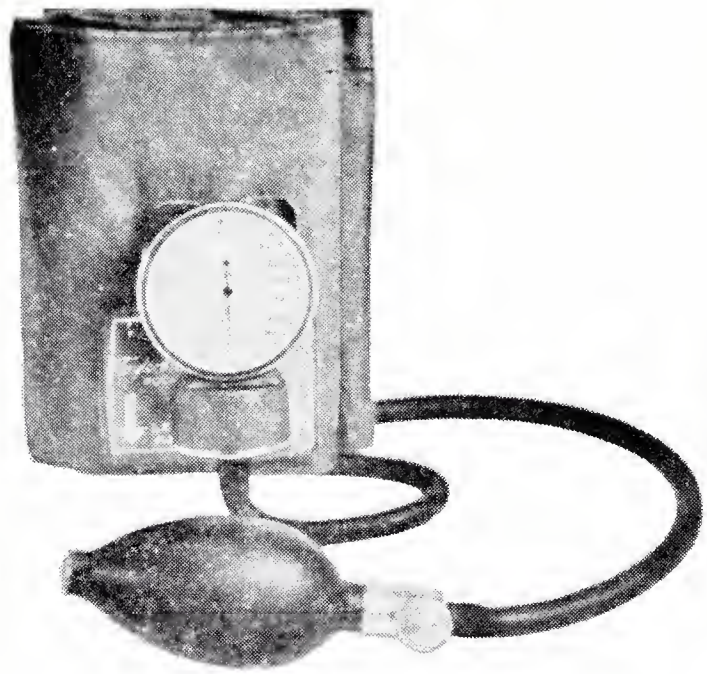

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Editorials

Think About It

If you went to your bank lately you probably saw a picture glaring at you with the caption "Now You Can Help!" It is a picture of children, victims of a civil war that raged Nigeria for over two years. That was the astonishing war furiously prosecuted in the name of politics and fuelled in part by journalists of the commercial press whose noble contributions ultimately made it impossible to sieve the false from the half-truths.

The dramatic end of that war must have been as much of a soothing relief for all Nigerians as it was for other people, especially Canadians who became emotionally wound up with the agony of the war, for diversified reasons. With assistance from the International Red Cross and the Canadian Red Cross, the Nigerian Red Cross is able to partly provide for the war victims, now that intra-national politics is irrelevant.

While the tendency to look far away for the "under-privileged and the unfortunate" remains high, the scope for service and assistance to the less fortunate is limitless right here in Canada. This is one thing the Canadian Red Cross understands. Its activities in this country are varied. This "community-conscious" generation of physicians and medical students should be interested in some of them.

The Canadian Red Cross comes forward with emergency food, clothing, bedding and shelter in cases of such family disasters as housefires.

Nurses in Outpost Hospitals and Nursing Stations serve the households of isolated areas.

The Sickroom Equipment Loan Service provides the free loan of essential apparatus for home care of the sick. Hospital visiting by volunteers brings friendship and company to hospitalized veterans. Red Cross Lodges offer recreational facilities for the veterans and overnight accommodation for their visitors.

The Red Cross Corps gives much needed assistance to veterans and their dependents, to the handicapped, to the blind, to crippled children, to some welfare patients and to the aged.

Red Cross Care in the Home courses are conducted by volunteer registered nurses.

The Water Safety Service provides instructor and pupil training programmes.

Women's Work is involved in the making of essential clothing and bedding for the underprivileged.

The one million members of Red Cross Youth carry out a large variety of tasks in the service of the community — from the operation of blood donor clinics to involvement in Indian community projects.

Last and maybe most important of all from the viewpoint of the hospitalized patient, the Society's National Blood Transfusion Service provides whole blood and blood products for any patient in any hospital in Canada at no direct charge to the patient.

March is Red Cross Month. For 61 years, the Canadian Red Cross has been operating, but only with the support and goodwill of people like you. Think about it. The Red Cross is always there.

You can always help!

Gratias!

In this last issue of the current volume of the Journal, the editor would like to express deep gratitude to those who volunteered their resources to make the publication viable in its forty-seventh year of existence.

We thank the Medical Alumni Association for the grant that made it feasible to have sizeable issues this year.

Several staff faculty members assisted some of the authors in various stages of the preparation of manuscripts. Special thanks are due to Dr. J. B. Walter of the Department of Pathology for providing materials and guidance for some of the Clinicopathological Conferences, and to Dr. Woody Fisher of the Department of Medicine for innumerable services provided prior to the publication of our issue on Liver.

The Assistant Editors were co-erced into meeting nearly impossible deadlines with proof reading. I hope we still remain friends!

Wayne Quan managed advertising with an ingenuity that almost reveals his Chinese heritage. Dave Ward who has been working on his assignment since last spring, and Barbara Kee his colleague, who was then hitch-hiking in Europe, both excelled as Circulation Managers.

Finally Joan Haglund deserves compliments for receiving all the cheques for the Journal and methodically "turning them over" to our creditors.

Thanks to all these people, editing the Journal has been a pleasant pastime this year.

T.O.

Guest Article

Saint Valentine--The Epilepsy Saga And The Birth Of An Institute*

WILDER PENFIELD
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Montreal, P.Q., Canada

My own approach to the study of epilepsy and through it, to the functional anatomy of the human brain, was a long journey — blind in the beginning, but somehow inevitable. I shall describe this journey as a "pilgrim's progress," although it may seem no more than a wandering tale of personal adventure in the outset.

We are told that Martin Luther was willing to "bet" *("drum wohlte ich schier wetten")* that it was no more than an aceident of sound that led epileptics to adopt Saint Valentine as their personal saint. He explained that "Valentine" and "Fallenden Sueht" sounded alike! Perhaps they do to the German ear when pronouneed by a German. But Luther, himself, had a fatal weakness for heresies, although his heresies, in faet, changed the whole history of Christendom.

I remain unconvineed and orthodox in the ease of St. Valentine. I prefer to eonsider him the patron saint of Epilepties. God knows the vast army of innoeent men and women and children who suffer from epilepsy in its many forms have always had need of a powerful ally. Many epilepties in that army are my friends. I owe them a remarkable debt of gratitude. For this reason, I have come to Copenhagen — to pay tribute to Saint Valentine before this distinguished Society that honours him, as well as to aeeept his prize.

Sir Charles Sherrington was Professor of Physiology at Oxford when I was a medieal student. He was always the student of funetion in the nervous system, always speculating on the "how" of integration. Later, during my hospital service in Boston, I watched Harvey Cushing in his surgical elinie at the Peter Bent Brigham Hospital. He was then demonstrating that neurosurgery could be made a respectable specialty with a low mortality rate. But, at that time, it was almost exclusively the surgery of tumours and of pain. For me, the great challenge in Medicine was Neurology, and yet I wanted to be a surgeon. Perhaps, I thought, a neurophysiologist in surgery might find a broader field.

With this in mind, the next two years were spent in graduate work — neurophysiology with Sherrington at Oxford, and, in London, neuropathology with Greenfield and neurology with Gordon Holmes and others. Then I returned aeross the Atlantie and beeame the neurosurgeon in the Presbyterian Hospital, New York. But it seemed absurd to be ealled a brain surgeon when I did not understand the healing of the brain when injured, or the formation in it of sears. I began at onee a part-time study of the healing of brain wounds in the laboratory of William Clarke, Professor of Surgical Pathology at Columbia University. We examined the resultant material under the microseope, knowing that such scars often eaused epileptie seizures. But I could not understand *what* I saw, to say nothing of the *cause* of epilepsy. After three years of this, I asked for six months off. Mrs. Penfield and I sailed for Spain with

*Excerpted from the Valentine Prize Lecture, delivered before the Danish Neurological Society and the Danish Epilepsy Association, June 20, 1967, Copenhagen, Denmark. Published in a slightly different form in Acta Neurologica Scandinavia, XLIII 1-10, 1967. Reprints obtainable from the Author.

our two children. In Madrid I studied the cytology of the brain with Pio Del Rio-Hortega and Ramôn y Cajal, and I stained the scars I had brought along with me, using their silver and gold methods.

It was clear, at last, how cells behave and where they come from during the healing and the scarring of the brain, but no clue appeared as to the cause of epilepsy. Aside from that, however, these methods had brought such wonderful clarity to the microscopic structure of the nervous system itself that I went beyond the scars, on my return to New York. In the end, with great enthusiasm, I even edited a three-volume handbook of cytology, written by many experts. It was called *"The Cytology and Cellular Pathology of the Nervous System."*

In the process of preparing this publication, I learned something important and unexpected. It was this: no single pilgrim crossing neurology's frontier could complete his pilgrimage alone. To come to "the place of understanding" there must be team-work. The team must have a common purpose, using many modern skills and many minds. In 1928, four years after the return from Spain, I moved to Montreal with a remarkably able colleague, William Cone. He was both a pathologist and a neurosurgeon. It seemed that it might be possible to form a team there and we had a plan — a dream, if you like.

But, in the meantime, my own particular problem was this: A brain-scar that produced epilepsy could be removed. This had been done from time to time by various surgeons in various ways. But could it be removed in such a way as not to disturb the function of the remaining brain? Would the removal not produce a second scar that would in time become epileptogenic and cause fits again? I had made many excisions experimentally, and I had done it once clinically while still in New York.

The patient was a young man who suffered from epileptic attacks following an injury. A falling brick had wounded the frontal lobe. After operation, his fits stopped. But was he cured? It would require many years and many more patients to decide that. Then I heard rumour that a surgeon in Germany was operating on epileptic soldiers, veterans with head wounds from the war of 1914-1918. The surgeon's name was Otfrid Foerster.

So, in 1928, six months before we were due to arrive in Montreal, my understanding wife and I transplanted our children, four in number now, to Breslau, Germany. Foerster, I found, had operated on a dozen such patients during a five-year period. He had published nothing about them as yet. Half of each block of excised brain and scar he had sent to Professor Wilhelm Spielmeyer to be studied by him in Munich. Spielmeyer, who was a very able neuropathologist, had evidently been too busy with other research. Consequently he had made no reports. Foerster turned over the material he had kept to me, and we set up a laboratory in the corner of a ward in the Wenselhanke Krankenhaus. The material was exactly what I needed in addition to the experimental animal scars of the past seven years and the excision from my first clinical case. I knew the needed microscopic methods well enough by then.

Foerster was a splendid neurologist, a careful surgeon, an excellent scientist and friend. So we had a wonderful six months of study together, and we published his twelve cases in complete detail. His clinical results had been good. When the work was summarized for publication, we had begun to look forward to the possibility of operation as a treatment not only when the local cause was trauma, but also when it was something other than trauma.

In the end what had we learned? — That surgical removal of a local area of brain, identified as the focus and cause of the epileptic seizures, was a promising method of treatment; that such operations are best carried out with the help of conscious patients under local anaesthesia; that gentle electrical stimulation of an area of irritable cortex (epileptogenic cortex) would produce the beginning of a fit; that pulling on the adhesions of a scar at such a site might do the same; that gentle electrical stimulation of neighbouring cortex could be used by the surgeon as a helpful guide to anatomical localization.

A hundred secrets about the nature and the cause of epileptic discharge remained to be discovered! But we had established new guidelines for the improvement of surgical technique. More than that, it was clear such operations could in the future provide a thoughtful surgeon with an opportunity to study the physiology of the human brain, an opportunity never even dreamed of in the past.

For my own part, a door was opening to an exciting future. As a graduate student in Sherrington's laboratory, I had hoped blindly to be able to use the methods of neurophysiology to reach some understanding of the human brain. But on arrival at the Presbyterian Hospital in New York there had been no opportunity or excuse for doing this. Patients were in need of practical care. So I had taken what seemed the first logical step for a young neurosurgeon — to become familiar with the histology of healing and scarring in the brain. That was something no one could teach me. And so (when not involved in clinical work) the seven long years in New York had gone to pathology and cytology. Study of the microscopic structures of the brain and the puzzling changes in brain scars had led me inevitably to the vast problem of epilepsy.

Perhaps, after all, when those years are viewed in retrospect, it was not so inevitable. Perhaps St. Valen-

tine, the Patron Saint of Epileptics, had had a hand in all this! Perhaps it was his scheme. In any case, an unexpected door had opened on the hoped-for opportunity. The good of my patients was about to justify, and even demand, large osteoplastic craniotomies in a search for the local cause of focal epilepsy. We could hope now to deal with the locally altered epileptogenic brain when the cause was trauma or tumour, and also when the cause was blood vessel abnormality or birth compression, or even infection.

This meant that I could turn back, at last, to neurophysiology as a method of approach. But it meant too that, more than ever, there was a need for the help of neurologists and radiologists and electrophysiologists and pathologists and chemists and physicists; also photographers and recording secretaries and newly-designed equipment. In short, what was needed was a neurological institute.

And that was the very plan that William Cone and I were formulating when we accepted the invitation to join the staff of McGill University and the Royal Victoria and the Montreal General Hospitals. In 1931, Dr. Alan Gregg, Director of Medical Sciences for the Rockefeller Foundation, agreed to help create an institute, and in 1934, McGill University opened the doors of her Montreal Neurological Institute — a place where patients could be studied and treated, a place for laboratories and workers with varied skills. Most important of all, there was a permanent endowment for scientific and academic work.

Epilepsy, the falling disease, the curse of the gods, had helped to build the Institute. More than that, it was the attack on epilepsy in that Institute that was about to open the doors of the operating room to neurophysiologists. In 1937, Herbert Jasper came to Montreal, bringing a rudimentary electroencephalograph with him on the seat of his car.

The pilgrim's progress had entered a new stage. From the time of my arrival in Montreal until I withdrew from Medicine in 1960, I no longer worked alone, but always as a member of a team. It proved to be a happy association, and if credit is due to anyone, it should include all of my many colleagues — too numerous now to name and scattered, as many of them are, about the world.

In the subsequent series of operations on conscious patients, electrical stimulation of the cerebral cortex with ever-improving stimulators became a routine procedure. What we learned about brain function in each case improved the accuracy of our cortical excisions and increased our ability to cure. On the other hand, what we learned about epilepsy, in each case, threw further light on brain function. We followed a standardized method of recording. (And Professor Theodore Rasmussen, the present Director of the Institute, and his associates are continuing those records to make them a living aid to research.)

Thus, as the years passed, we mapped out the functional areas of the human cerebral cortex: a) the previously recognized sensory and motor areas; b) certain new cortical localizations such as vocalization-control, supplementary motor area, and supplementary speech area; also gustatory and gastro-intestinal representations; c) numerous new details in regard to the conditioning of motor, sensory, or physical mechanisms; d) a clear understanding of the initially uncommitted cortex of the temporal lobes.

The adult uses a part of this uncommitted cortex during the thought transactions of the speech mechanism. The rest of it, including the area that might have been developed for the purposes of speech in the lesser hemisphere, comes, in time, to be devoted to perception.

Epileptics have long told those who would listen (as the great Neurologist Hughlings Jackson did) about these things. And we must bear in mind that anything a gentle electrical impulse can do, a localized epileptic discharge at that point in the cortex can do as well. In the Montreal Neurological Institute, epilepsy has been the great teacher. To the Patron Saint of epileptic patients we have a deep sense of gratitude. Without the help of gallant and intelligent patients, we would have been without a guide in our expeditions of discovery. What little we have concluded as a team we have also tried to publish for the benefit of all such patients and, we hope, for your use in Neurology.

The last time I saw Sir Charles Sherrington, he had passed his ninetieth birthday. But he questioned me about my experience with electrical stimulation of the cerebral cortex of conscious patients. He was, I think, a little envious of my great opportunity. He asked particularly about the physical responses that sometimes follow stimulation of the temporal lobes. It causes, as you may know, flash-backs of previous experience to come to conscious patients. All that the patient was conscious of, in an apparently forgotten strip of time, comes back to him. The stream of consciousness flows again as it did long ago, although he knows he is really in the operating room.

But I must not become technical in this essay, and so I shall omit here the discussion of brain mechanisms included in the full text of this address.[1] Many scientific observations to which epilepsy opened the door were summarized in the Sherrington Lecture at Liverpool in 1958. It appeared as a little book, the title of which was "The Excitable Cortex in Conscious Man[2]."

Electroencephalographers, neurophysiologists, psychologists, radiologists, and clinicians alike must recognize that epilepsy has something to teach us all. Patients who suffer from cerebral seizures should be classified, as well as possible, as to cause, and also as to location of

the originating neuronal discharge. In all this, we must all have due respect for professional teamwork.

The taking of the history is the most important step in the analysis of any case of epilepsy. It calls, too, for the greatest skill of all. Friendship and clear understanding between doctor and patient are prerequisite to the doctor's success — prerequisite also to the patient's happiness. St. Valentine smiles on doctors who have an open mind and who understand the meaning of compassion. He smiles on men who can learn from epilepsy and who help the epileptic.

Neuro - scientists have done much to make the public realize that epilepsy is not a mysterious curse but a disease like other diseases that man is heir to. It can be cured or controlled, and the sufferer can hold up his head today and be a useful, happy member of society. The doctor's primary role may be to treat disease, but the best doctors of medicine are more than specialists. They help their patients to face life, help them to be good citizens, and in so doing, play the part of good citizens themselves.

I have told you the story of a medical "pilgrim's progress" — an account of the wandering of one neurological pilgrim who hoped to find "the place of understanding." I have told you how he came upon the great teacher, Epilepsy, and mentioned some of the things he learned.

Epilepsy teaches in a language all its own. We must learn to listen and to translate what it is telling us. Hippocrates, the Father of Medicine, did this, for it was in his treatise on epilepsy, "The Divine Disease," that he remarked:

"The men of our day who undertake the cure of this disease . . . with superstitious regimens are no better than magicians, charlatans, quacks! . . ." Then he added:

"The sacred disease, and madness too, come from the brain when it is not normal . . ."

Epilepsy and madness will be problems for physicians to face always. That will be the day's work for the doctor. But let them not be content "to do the day's work well and not bother about tomorrow." Beyond the day's work lies our great opportunity. Beyond "epilepsy, and madness too," lies the most difficult and important problem science has to face — the relationship of the brain to the mind, the body of man to his spirit. Man, after all, is the problem of our profession. In conclusion then — Let hopeful discontent long continue to drive each of you and all of us on a pilgrimage of his own. Every pupil of epilepsy, the great teacher, will have something to add.

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1. "Epilepsy, the Great Teacher: The Progress of One Pupil." Acta Neurologica Scandinavia. 43:1-10, 1967.
2. "The Excitable Cortex in Conscious Man." Liverpool University Press, 1958; also Charles C. Thomas, Springfield, Ill., 1958.

Awards '70

THE WEBSTER PRIZE

Won by **Frank G. Sommers** for the originality and literary style of his fascinating article, *The Influence of Social Experience On Men Of Science — A Historical Perspective*, pages 170-172 of this issue, the prize is fifty dollars.

Each year all student contributors to the Journal are eligible for this award. Selection of the best article is made by the Academy of Medicine and the prize, endowed by Mrs. Annie Webster in memory of Dr. J. D. Webster, is presented annually at the Academy of Medicine Library and Historical night (April 7, 1970).

THE R. I. HARRIS PRIZE

For his article, *Back Trauma*, published in the November issue of the Journal, **R. W. Zeindenberg** has been awarded the R. I. Harris prize.

The prize carries a cash value of one hundred dollars. It is available annually to the best article written by an undergraduate on a topic related to Orthopaedic Surgery, and published in the Journal.

Selection is made by the training committee on Orthopaedic Surgery.

We congratulate the prize winners and thank the Academy of Medicine and the Training Committee on Orthopaedic Surgery for encouraging undergraduate journalism and scholarship.

Editor

History Of Medical Education In Toronto

J. David Beatty, B.Sc., 7T0

'Tis all a checker-board of Nights and Days
Where destiny with men for pieces plays:
Hither and thither moves, and mates and slays,
And one by one back in the closest lays.

OMAR KHAYAM

1. *Background:*

It was Hippocrates, back about 400 B.C., who laid the original foundation of what we now know as the practice of medicine. He had an ideal of competence embroidered with a code of ethics that might well be considered the genesis of modern science, for it was based on accurate bedside observation, curiosity, open-mindedness and clear reasoning. But "the forces in man and in society making for rigid conformity and intolerance may work in much the same way in any age, whether in theology, politics or investigation of the ways of nature. The spirit is the same; it just changes its locale in human affairs."[10]

By the time of the mediaeval university, the professors literally preached their lessons in medicine with inflexible authority. Learning on the part of the students was for the purpose of defending dogma at examination and for centuries academic medicine excluded the passing of experience directly from practitioner to student.

The cracking of this rigidity in medical education has been an ever increasing process over the past four centuries drawing on successively enlightened foci in Italy, Leyden, Edinburgh, Germany, Baltimore and Cleveland.

2. *King's College – Faculty of Medicine – 1843-1853:*

In the early days of Canada's recorded history such medical care as there was, was given by medical officers attending the garrison or the navy. Its quality was poor. As the land became settled there developed itinerant and incompetent physicians that dispensed wives' tales and frontier remedies to a colonial populace that was constantly challenged by contagious disease.

By 1818 the Medical Board had been established in an effort to control quality and licensing. In Lower Canada the first medical school was opened in Montreal in 1824 and it soon became associated with McGill University. It was that same year, 1824, that Sir John Rolph started a school in St. Thomas. Although Rolph was a driving force in medical education in Upper Canada for fifty years, his first effort survived only two years and then collapsed.

In 1828 the Council of King's College undertook preliminary negotiations for the provision of a medical school in Toronto. Sir John Colborne, then the Chancellor of King's College, felt that there were insufficient funds available and doubted that medicine was attractive enough in Upper Canada to warrant parents sending their sons to a medical school. Without students there could be no school and the idea was dropped.

In 1837, under a new Chancellor, Sir Francis Bond Head, the Council of King's College again considered a medical school. The whole field of university instruction was to be divided into six departments, Medical Science being one. The department was to be run by professional men, one professor and three lecturers, that resided outside the university. The teaching was to be arranged so that it did not interfere with private practice and an annual salary of two hundred pounds was to be given to each lecturer. Just as the plan was to be implemented the Rebellion of 1837 broke out and again operations were halted, but this time the idea did not die.

In July of 1839 the College of Physicians and Surgeons of Upper Canada applied to King's College for aid in establishing a medical school. Although help was refused on the grounds that this lay within the realm of university education for which King's College was provincially responsible, it appears to have been the necessary stimulus for the setting up of a university medical school.

In February of 1842 the King's College Council apportioned some funds to the Toronto General Hospital to augment their number of teaching beds and in June of the same year Dr. Christopher Widmer presented a report to the King's College Council recommending a Faculty of Medicine composed of four equal departments and drawing heavily from the best talent in Great Britain for personnel. By July Dr. Henry Sullivan was appointed Demonstrator of Anatomy and Curator of the Museum. In November of 1843 the King's College Council adopted a more detailed plan for the setting up of a Faculty of Medicine. There were to be six departments and an annual stipend from King's College. The six departments were: Practical Anatomy; Anatomy and Physiology; Theory and Practice of Physic; Principles and Practice of Surgery; Midwifery and the Diseases of Women and Children; Materia Medica, Pharmacy and Botany. Each professor was to receive an annual salary of two hundred pounds except Anatomy where the salary was two hundred and fifty pounds. At Toronto General Hospital eighty beds were set aside for medical and surgical teaching and separate puerperal accommodation was provided.

In order to sit the final examinations a student was required to be twenty one years old, have spent five years at University, three of which were occupied by attendance at medical lectures. Admission requirements were either Faculty of Arts "testimonium" of six successful terms (two years) or for those over twenty one

years of age a matriculation in Greek and Latin Classics and in Mathematics. The curriculum was divided into six-month courses in each department and the students were to attend one or two of these lecture series; and observe the medical and surgical practice on the wards and the clinical lectures in the Toronto General Hospital for eighteen months. There were three degrees that could be given: M.B., M.D., and C.M. (Chirugiae Magister).

The first lectures in this new school were given on January 15, 1844 and in the first session there were only two students. By the session of 1852-3 there were sixty students in the school, a medical building (Moss Hall), and a strong faculty was being acquired.

It was at this time that the Upper Canada Legislature adopted the Hincks Act which abolished the concept of a university medical faculty. The espoused philosophy was a belief that the public should not be responsible for training men for a such a lucrative profession. It may well have been the state's method of condemning the church and demanding secularization of the universities (King's College was associated with the Church of England). However, according to Primrose[16], the most plausible explanation is that the government was dismayed by the prospect of the expenditures necessary to support a medical school. "This lame expedient led to the multiplication of schools, and to defective training."[17]

3. *The Proprietary Schools 1853-1887:*

After the collapse of Rolph's school in St. Thomas, he moved to Dundas where he set up a combined medical and legal practice, but no school. Rolph fought beside William Lyon MacKenzie in the rebellion of 1837 and following their defeat was forced to flee into exile in the United States for several years. After his return to Canada, he set up a medical school which, in 1851, was incorporated by the Legislature as the "Toronto School of Medicine" – the school for "medical students who do not intend to enter the university."[3] It was during that same year that the Toronto School of Medicine became associated with the Methodist College, Victoria University.

In 1850 the "Upper Canada School of Medicine" was established. In 1851, under the leadership of Bishop Strachan, a charter was taken out for Trinity University and the Upper Canada School became the "Trinity Medical School".

Thus in the early 1850's there were three medical schools in Toronto, each one using the facilities of the Toronto General Hospital. Great rivalry and even hostility developed, especially between Strachan and Rolph. Strachan, on one occasion, gained control of the General's Board of Trustees and dismissed a number of the lecturers of the Toronto School of Medicine until they resigned from Rolph's staff. They were then reinstated at the Toronto General Hospital.

The Hincks Act of 1853 terminated the short life of the King's College Faculty of Medicine. In 1856 some of the professors of the Toronto School of Medicine, through a litigation procedure, gained control of the school from Rolph and moved into the recently vacated Moss Hall. Despite the loss, Rolph continued to operate his medical school at Victoria University. In the same year, 1856, the Trinity Faculty openly opposed the Hincks Act and aroused the wrath of Strachan. The end result was the resignation of the professors and Trinity Medical School remained dormant until 1871.

Despite the Hincks Act and general public sentiment against supporting the medical professions, between 1853 and 1871 the considerable sum of $65,000 was granted to Upper Canada Medical Schools. In fact, all schools that applied during that period received grants.

One of the most unfortunate results of the keen competition between the different schools occurred in 1868 when the animosity reached such a pitch that the Toronto General Hospital, unable to function properly, was forced to close down for a year. This led to the loss of a number of distinguished physicians, and many would-be doctors. The most notable of all these was the young William Osler, then only twenty, who eventually went on to Baltimore where he was a dynamic force in revolutionizing medical education.

In 1870 Rolph died. By 1871 a number of the Victoria University staff had resigned and were responsible for the resurrection of the Trinity Medical School. Although Rolph's school struggled on, in 1875 the students deserted en masse to the Toronto School of Medicine.

The increased stress on basic science that was emanating from the German schools put a new financial burden on the proprietary medical schools. By remaining independent and lacking a strong financial base (state, denominational or industrial), the proprietary schools were unable to build the necessary laboratories and equip them. Accordingly, the scientific standard fell. Although the university had not taught medicine since 1853 it still held the examining privileges and in 1882 when an effort was made to raise the quality of graduating physicians the size of the class dropped from thirty-five to fifteen in one year, and eventually to only ten.

4. *The Faculty of Medicine – Building, Consolidation, Eminence – 1887-1910:*

With the elevation of the standards by the university the financial problems of the proprietary schools became acute. In 1887, the Faculty of Medicine of the University of Toronto was re-established and the staff of the Toronto School of Medicine became the staff of the new university school. With this larger financial base the growth of the faculty was dramatic. By 1892 there

were thirty-four staff and two hundred and eighty students and in 1902 there were fifty-six staff and four hundred and thirty-two students. The increase in size of the classes coupled with the steadily rising emphasis on better equipped laboratories for anatomy and physiology indicated the need for more facilities. In 1903 the new Medical Building was opened at the exorbitant cost of $125,000 and was furnished with $50,000 of equipment. The 1905-6 session saw a school with six hundred and seven students.

"The statute governing the reorganization of the faculty was constructed so as to provide for a reconsideration of the appointments to the staff every five years. This in fact meant that a fresh reorganization was to be brought about at stated intervals, and that all appointments were to lapse when the term of five years had expired.

In 1897, when a reorganization became due, the whole question of the relationship of the Faculty of Medicine to the University of Toronto was very thoroughly considered, and it was determined that the policy which had been in existence for ten years should be abandoned, and that the appointments to the staff should now be made permanent without any arrangement for further reorganization."[16]

Although it is regrettable that the era of change came to such a rapid and final close, as we shall see, it did stimulate significant progress in the Faculty. There was a scientific awakening and the realization that the future of medicine depended on research. In 1890 Ramsay Wright went to visit Koch's laboratories in Berlin with the expressed intention of setting up similar facilities in Toronto. Toronto was becoming progressive but "innovation in Canadian medical education has been neither frequent nor original."[10]

In 1903 the Medical Building was completed and in the same year, as part of Trinity University joining the University of Toronto, Trinity Medical School amalgamated with the Faculty of Medicine. It is interesting to note that neither Trinity nor Toronto had allowed women to register in medicine. The Ontario Medical College of Women thus appeared in 1883 and although attempts were made, it was not allowed to amalgamate in 1903. The Victorian values were, however, on the wane and the Faculty made the following concession: "That in view of certain prospective changes which are suggested in connecting with the method of providing instruction in Medicine for Women in Toronto the Faculty of Medicine of the University of Toronto is now prepared to register female students in Medicine, and agrees that whatever arrangements are deemed necessary should be made for their instruction."[17] By 1906 the Ontario Medical College of Women was no longer in existence, its staff and students having blended into the university school.

Following the amalgamation in 1903 the Faculty turned its efforts towards raising the entrance standards as these had fallen miserably in the proprietary school era. The requirements by 1912 had been raised from 33% on half the papers in junior matriculation (grade 11) to passing all the senior matriculation papers (grade 12), and in 1908 the medical course was lengthened from four to five years.

In 1906 the Royal Commission on the University of Toronto reported. They emphasized the necessity for fuller Faculty, as opposed to University, control of the curriculum and strongly advised the government of the need for good medical research and, because of its benefits to the public, their financial obligation in sponsoring this work.

In 1910 the famous Flexner report was published. It outlined three basic principles: medical education must be in a university setting, medical schools must be staffed by full-time teacher-investigators, and teaching hospitals must be under university control. Toronto certainly was a university school, they were well aware of the need for full-time and fully-endowed "chairs",* but the Faculty could not and never did gain control of the teaching hospitals. An attempt had been made back in 1843 to gain control of the Toronto General Hospital by the King's College Council and another attempt was made in 1911 by the Faculty of Medicine Council. To compound the situation in the few remaining years before the war the Hospital for Sick Children, the Toronto Western Hospital, and the Saint Michael's Hospital all became affiliated with the Faculty as teaching hospitals. In 1969 the report of the Independent Planning Committee was still attempting to grapple with the results of this failure.

But in 1910 Toronto was one of 'THE' medical schools on this continent. Flexner himself writes: "In the matter of medical schools, Canada reproduces the United States on a greatly reduced scale. Western University (London) is as bad as anything to be found on this side of the line; Laval and Halifax Medical College are feeble; Winnipeg and Kingston represent a distinct effort toward higher ideals; McGill and Toronto are excellent. The eight schools of the Dominion thus belong to three different types, the best adding a fifth year to their advantages of superior equipment and instruction."[5]

5. *The Modern Era – Loss of Direction – 1910-1939:*

The recommendations of the Flexner Report revolutionized medical education in North America with John Hopkins setting the pace and providing the example. Toronto headed into this era in good condition and had its sights aimed in the progressive direction. In 1912 the Medical Research Fund was established in Toronto

* The first full-time clinical chair in Canada was the Eaton Chair in Medicine established in the Faculty of Medicine, University of Toronto in 1919. It was also one of the first full-time clinical chairs in North America and was followed in two years by a full-time chair in Surgery.

as a private-contribution organization to sponsor clinical medical research in the Faculty. The Dean, C. K. Clarke emphasized the necessity for the research in this way: "Every teacher of medicine or of any living science knows that, while in the first place he has to instill the principles that have been established by the work and experience of his predecessors and contemporaries, it is hardly less important to instill also the spirit of enquiry, and to train his pupils to test critically their own ideas and those proposed by others. The proper outlet for an enquiring mind is the critical training of systematic experimentation."[15]

In 1913 the Connaught Antitoxin Laboratories were founded by A. G. Fitzgerald who had had extensive experience in this area at Harvard and California. The idea of the laboratories was that they work with the Public Health Authorities in providing anti-type biological products at cost and that they undertake extensive research in the future.

In 1916-17 the Board of Governors of the University allocated $15,000 for medical research and by 1920 this had grown to $60,000 annually. In 1919 Colonel Gooderham provided the funds for a laboratory to do fermentation research.

And these efforts were rewarded, more handsomely than anyone would have imagined. In the summer of 1921 Banting and Best discovered insulin. "Toronto, a quiet provincial university with a good medical school, suddenly became a mecca for experts in diabetes from all over the world. There can be little doubt that no discovery and no two persons have ever brought so much fame and fortune to the medical faculty."[4] Yet in some respects this may have been detrimental to the development of the Faculty as a whole. Certainly research money was easier to obtain in Toronto than anywhere else in the country, but the relative ease with which the discovery appeared to occur, the clinical trials of the new product and the circumstances of the Nobel Prize all seemed to cause friction between different segments of the Faculty. Whatever the reason, the Faculty was unable to adopt an organization pattern for school and hospital to facilitate the pre-eminence of scientific pursuits and to foster interdisciplinary research. They certainly were not aided by the economic situation, either following the war or in the depression, nor by the general university attitude at that time of portraying Toronto as an undergraduate school and encouraging the pursuit of graduate work at more progressive centres, thereby stifling the spirit of enquiry.

The net result was that three different approaches developed. On the one side was the Banting Institute, the School of Hygiene and the Connaught Laboratories geared for medical research. On the other side was the Department of Surgery which, apart from developing 'living sutures' was geared towards the production of practical surgeons and to this end introduced the well known "Gallie course". In the centre the Department of Medicine was trapped with insufficient funds and thus an inadequate post-graduate programme.

Somehow the cornerstone of the practice of medicine became clouded and the desire to maintain an academic standard of excellence predominated. The course was lengthened from five to six years, the admission requirements raised, and all students were given the more academic M.D. degree. "The greatest emphasis at the University was in the passing of examinations . . . The practical as it pertained to the practice of clinical medicine was almost totally ignored. The viewpoint was that one would learn all this later in an internship or in actual practice . . . Internship was not compulsory nor indeed was it encouraged."[19]

Ironically, the university felt that it should have more control over the licensing of physicians at the same time as it was becoming more separated from the routine practice of medicine. In 1936 when the Ontario College of Physicians and Surgeons accepted the Medical Council of Canada Examinations as satisfactory for licensing we read in the President's Report: "Now remains the development and adoption of a plan acceptable to the Council, the College and the Universities in this province, whereby university degree and certificate and licensure may be obtained by passing one and not two sets of examinations."[15] The Faculty seemed unaware of the responsibility that they would be undertaking in doing this and that in thirty years the medical schools would be desperately grappling with their failure to meet the needs of the practising physician.*

6. *War – 1939-1945:*

War, as had been found between 1914 and 1918, had many advantages and disadvantages to the medical school. The full-time staff was drastically reduced and the funds available to the school were slashed. But in return the surgeons got excellent training and practice and the researchers, although more directed and restricted were much more prolific and well-endowed.

In the Thirties a special Arts and Science course directed at providing better exposure to the basic sciences and the scientific method was established. On completing this course the students could go on into the clinical portion of the medical course. This would have been a good pilot project that might have lead to numerous changes in the medical curriculum; but with the war, the course (Biological and Medical Sciences) had to be discontinued.

The only major alteration in the course in over twenty years occurred during the war. By shortening the fourth year and using the summer vacation for

* In 1950 a system of Medical Council of Canada examinations was instituted that covered the granting of the university degree, the certificate and licensure.

medical teaching, the course was decreased by the better part of a year. Although some attempt was made to retain this procedure following the war, the old system was revitalized.

When staff returned following the war, many of them expounded the virtues of the military system of specialist units (e.g. Cardiovascular). A number of attempts were made to have the hospitals and medical schools oriented around this principle, but to no avail. Many of the more progressive hospitals did, however, begin to internally organize around the unit concept. It is interesting that over twenty years later when the Faculty did eventually revise its curriculum, it was this system method of teaching that was chosen.

7. *Specialization and Research – 1945-1950:*

During this period the Faculty had its first full-time Dean, J. A. MacFarlane. Under his direction the facilities of the Medical School 'mushroomed' and by 1950 it was said that: "The school now has the doubtful distinction of being the largest medical undergraduate training centre on the continent."[15]

It was also during this time that a number of paramedical courses were instituted* and that a boom in post-graduate medical education occurred. "It had been the custom for graduates from the faculty, who desired further training, to seek it abroad, usually in the British Isles. As late as 1939 young men, who wished to become specialists in a given field were being advised by the heads of departments to go to England for training. The links with the teaching heads of universities there were close, and a word from the professor of a department usually resulted in a posting to a colleague's institution in London or one of the other British universities."[4]

Within twenty years the situation had reversed and five-sixths of the graduates indicated their intention to go into post-graduate work and the majority of these stayed in Toronto for these studies. The post-graduate school became as large as the undergraduate school, although not under university jurisdiction. Whereas, in the early 1900's the staff of the Faculty of Medicine had only to teach undergraduate medical students and maintain their practices, by 1960 they were being called on to teach twice as many students again in other courses or in graduate work, to direct research work and carry on practices.

We need not go into all the details of the physical growth of the medical school, suffice it to say that in a fifteen- to twenty-year period the facilities of the Faculty and those institutions associated with it multiplied remarkably. This growth and the strong emphasis, both academic and financial, on research and post-graduate work lead to a de-emphasis of undergraduate medical education. In fact, no major permanent change occurred in the medical curriculum after 1919.

This is the period that epitomizes what Lamontagne has called the "industrial or modern era". It was concerned with the building of affluence and as such was a static era. He states: "Know-how or professional training, the main commodity on which universities concentrated during the industrial period, will become obviously the most perishable, the less meaningful and even, at least in the long run, the less useful form of knowledge."[7]

The student had become caught in a double bind; on the one hand he was told that he must only master basic concepts and it was the scientific approach that was necessary, and on the other he was assessed and valued on his mastery of detail and know-how.

8. *The Post-Modern Era – 1960-1970:*

It was back in 1950 when Sidney Smith noted that; "while professional schools in the main prepare their students for their occupations, professors in the humanities and social sciences can assist in preparing them against their occupations."[15]

Around 1950 Western Reserve revised their entire Faculty structure and undertook a new approach to undergraduate medical teaching. In the late Fifties and early Sixties the Faculty at Toronto made a number of token attempts to confront this problem, but without success.

To go into many of the soul-searching suggestions and critical articles that have arisen over the past ten years would require a short novel. Suffice it to state that in 1969 a "New Curriculum" was instituted at the University of Toronto, Faculty of Medicine. It is a combination of block and systems teaching and is capped off by a clinical clerkship. Perhaps it was instituted as an effort to again raise the academic standard of the undergraduate instead of: "To teach medicine as a coherent, meaningful whole, rather than a series of unrelated disciplines and to give the student from the beginning of his medical education a feeling for the central purpose in medicine, to deal helpfully with patients."[10]

But there is no doubt that as a result of the change many questions are being asked and the very foundations of medical practice and medical education are being subjected to close scrutiny.

> "The continued growth of technological civilization, indeed its very survival, requires an enlargement of our understanding of man's nature. Medicine was, at the beginning of civilization, the mother of sciences. Today it has once more the opportunity of becoming a catalytic force."
>
> RENE DUBOS (3)

* 1946 – Physical and Health Education course for training high school teachers.
* 1949 – Division of Rehabilitation Medicine courses in Physical and Occupational Therapy and later Speech Therapy.

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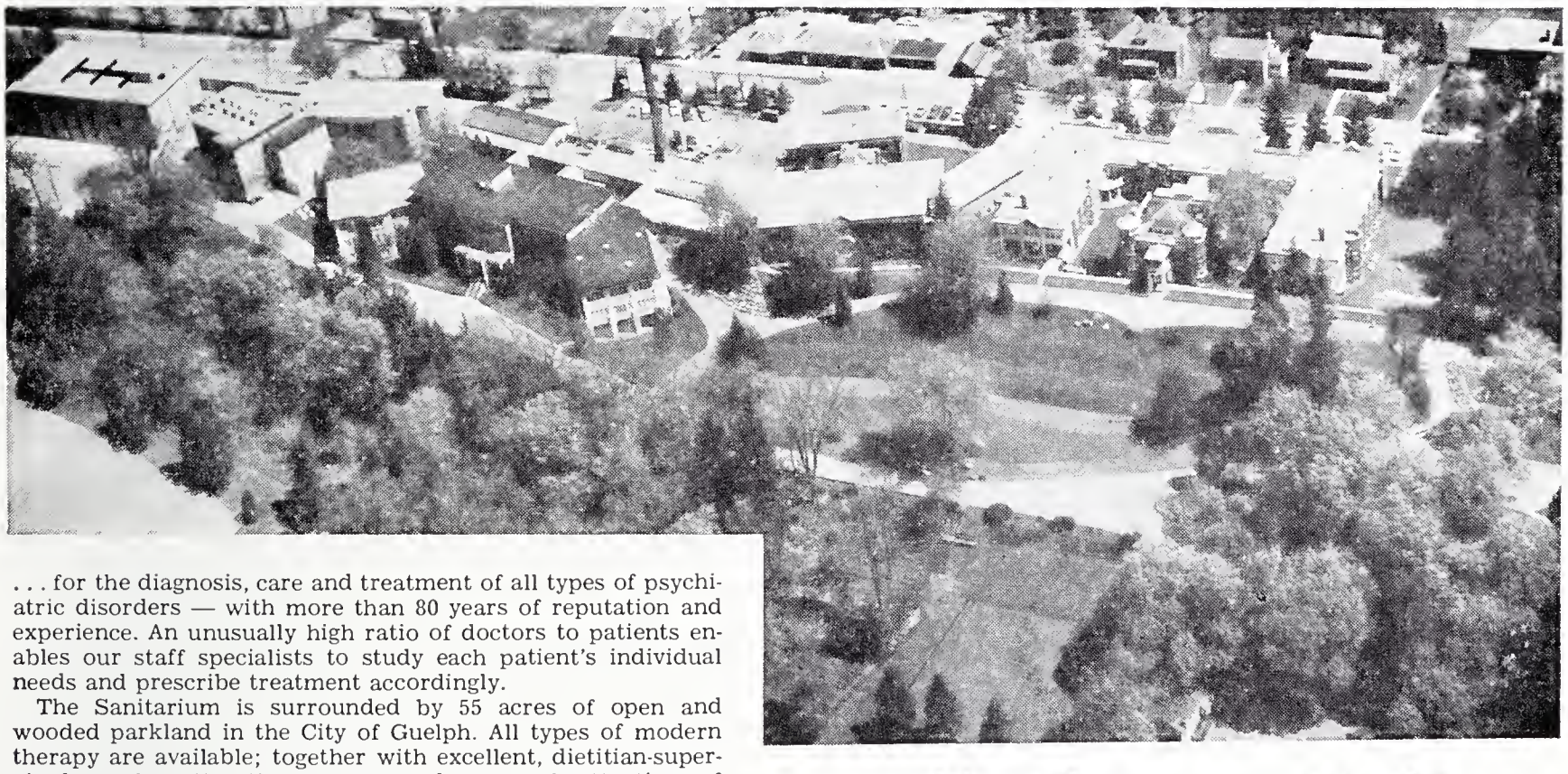

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Materia Medica

W. A. Roy, 7T0

Down through the ages man has dealt with disease in a manner befitting the then accepted theories of causation. This article is divided into two sections – a) an odyssey through the various eras of medicine, concerned specifically with theories of etiology and their respective modes of treatment, and b) a detailed history of some of the more commonly used modern materia medica.

PART I – AN ODYSSEY

Egyptian

The journey begins on the banks of the Nile approximately 5,000 years ago. In Egypt there existed a very close link between religion and disease. A sick person was either possessed of a demon or was being punished for incurring the wrath of the gods. If disease was due to the presence of a demon, why not drive it out? Or if the gods were angered, why not offer prayers of appeasement? The Egyptian system of gods provided doctors with a patron diety, Thoth, who gave to the physician the "skill to cure". Possessed of this great gift the Egyptian physician developed many rituals – incantations, prayers, and magical potions. Many of these potions were foul-tasting concoctions which, it was reasoned, would prove distasteful to evil spirits and drive them away. By chance, certain substances were found that did indeed produce a cure and these were deemed efficacious against a specific demon. Since these preparations were usually mixtures of many substances (animal, vegetable, mineral) the beneficial ingredient often went undetected. As has happened throughout history, however, these drugs came to be used in conditions where they had no effect, and their often lethal side effects led them into absolute disrepute. While the modern day physician might marvel at the invocation of gods to aid in healing it is interesting to note that he too, albeit unwittingly, invokes the aid of Horus, the protecting deity against noxious animals, every time he writes a prescription. The Rx on every prescription represents Horus' eye.

Greek

We now shift our attention to the land of the Greeks. As in Egypt, superstition played a large role here. Much of Greek medicine was carried on in the temples where divine aid was felt to be at hand. Just as the Egyptians had before them, the Greeks deified one of their physicians, Aesculapius. He is pictured as the wise old man holding in his hand a staff around which a serpent entwines itself. To this day, despite its connection with the supernatural rather than with rational medicine, the snake entwined around the staff is the symbol of the profession of healing.

There was, fortunately, another side to Greek medicine. This is symbolized by that group of men who questioned the superstitious rituals and approached disease with a more questioning, open mind than ever before. These men felt there was a natural explanation to disease, and that sickness, like other daily occurrences, could be understood on the basis of natural laws. Take for example the theory of Anaxagores, who believed that four elements -- earth, air, fire and water, were related to everything. Empedocles enunciated his own theory – blood was hot; phelgm, cold; black bile, moist; and yellow bile, dry. Since all diseases were due to an imbalance, a cold was treated with a hot remedy, fever with a cold one, etc.

We come now to the most important Greek in medical history – Hippocrates. His contribution to medicine can best be described as a renunciation of theology and much of philosophy, which had at this time replaced observation with doctrine. He used his great powers of observation to detect patterns of disease, made careful records, and was one of the first physicians who concerned himself with the course of disease and how this affected the prognosis. His case records were set down with complete objectivity, modesty, and honesty, all failures included. "I have written this down deliberately," said Hippocrates, "believing it is valuable to learn of unsuccessful efforts and to know the causes of their failure." This new approach was in itself no mean accomplishment.

Although Hippocrates knew the use of many drugs he believed in "the healing power of Nature" and was sparing in his prescriptions. He adopted the "expectant" line of treatment, realizing that the natural course of many diseases was to burn themselves out. He thus showed great concern for making his patient as comfortable as possible during his illness, placing great stress on nursing care and diet.

Roman

The greatest contributor to Roman medicine was the Greek Galen. Unlike Hippocrates, Galen was concerned with his image as a great physician and stated his beliefs as infallible proclamations. During his lifetime Galen wrote over 300 books on physiology, anatomy, and drugs. Like his Greek predecessors he believed in the four humors. His teachings in anatomy were based on animal dissections and not on human specimens. His works are full of superstition, but the amount of factual observation and common sense suggests that this was deliberate and that the corruptions were designed to suit the times.

It is ironic that Galen, the man who might have advanced medical inquiry, was responsible for its sudden

and unfortunately prolonged stop. Because his writings contained so many facts, and because he was so arrogant in his presentation of them, Galen's works were accepted as the truth by influential circles for centuries to come. Galen's authority during the next thousand years was due to the fact that in philosophy he was a monotheist. He taught that all structures in the human body were formed by the Creator for a known and intelligible end. Such teachings were acceptable to the religions of both Christendom and Islam, and so, were assured of support for centuries to come.

Dark Ages

Following the overthrow of the Roman Empire we enter that period during which there was little in the way of scientific progress. The thinking man was replaced by the believing man, and learning was synonymous with memorizing Galen's teachings without question.

With the rise of Christianity came a resurgence of the relationship between medicine and religion. St. Augustine, in the 5th century had said: "All diseases of Christians are to be ascribed to demons, chiefly do they torment the freshly baptized; yes, even the guiltless new-born infant." The belief that sickness as well as good health was under the direct control of God led to an increasing dependence on prayer and faith-healing. Here is a return to the medical practices of ancient Egypt and a rejection of the Hippocratic teachings. Implicit faith in divine mercy made inquiry into the causes of disease unnecessary and even culpable. The doctor who cured patients by rational methods of his own devising, actually meddled sinfully with God's designs. In the view of the early Christian Church the employment of drugs implied a lack of faith, and medicine itself was considered a godless science. In such an atmosphere it is little wonder that the questioning mind stagnated.

Renaissance

History makes a pattern of repeating itself, and just as the science of discovery was replaced by the science of believing, so the latter was once again overthrown by the questioning minds of a few brave men who dared to challenge accepted teachings.

Leonardo da Vinci is not most commonly remembered for his contributions to medical science. But here, as in so many other fields, he made great discoveries and cast new light on long known misinterpreted facts. He courageously went against the Church's decrees by dissecting the human body and gaining first hand information in anatomy.

Another brave anatomist was Andreas Vesalius. It has been said that modern medicine began with the publication of his textbook of anatomy – *"De Humani Corporis Fabrica* (1543)". It opened the way for true physiology based on actual, observed anatomy rather than on the unfounded assumptions of Galenic physiology.

"Paracelsus was the Luther of medicine, for when authority was paramount he stood out for independent study." – Sir Wm. Osler

We now come to a man who played a great part in directing medical science in the direction it has taken. Paracelsus (1493-1551) was, in all senses of the word, a rebel. At a time when heretics and their works were being burned, he, as professor of medicine at Basel, took the hallowed works of Galen and burned them in the city square. Paracelsus' greatest contribution, and the one we are most concerned with here, was his role as the founder of modern chemotherapy. Alchemy, according to him, was "neither to make gold nor silver but to take the supreme sciences and to direct them against disease." Here then was the first enunciation of what has come to be such an important principle in modern medicine. Paracelsus himself introduced many metals to the Western pharmacopoeias – mercury, sulphur, lead. During and immediately after Paracelsus' life new drugs were being introduced from North America. Paracelsus was a leader in the recognition of the value of some of these substances. In 1577 the English translation of a Spanish herbal appeared under the title "Joyfulle Newes out of the Newe Founde Worlde." In it are mentioned such drugs as ipecac and cinchona.

Space does not permit the inclusion of many of the great advances made during the 16th, 17th, and 18th centuries in the long march toward the theory of natural causation. The works of William Harvey, Anthony Leeuwenhoek, Marcello Malpighi and many others left the old Galenic theories of physiology in ruin. The doctrine of the circulation of the blood and the new advances in chemistry accorded ill with the old humoral pathology which ascribed all disease to excess or defect of one of the four humors. The falling from favour of the Galenic physiology was the major step on the road to our present day knowledge. Many variations on basic tenets were introduced, but the fundamental doctrine of natural causation was becoming firmly entrenched.

One area of modern medicine that we cannot skip over is microbiology. It is obvious to us today that micro-organisms cause disease, but less than one hundred years ago virtually nothing was known of this vast field. Indeed there was great debate over the source of bacteria, with many knowledgeable and influential men supporting the theory of spontaneous generation. Two men must be mentioned here for their work in this field. Louis Pasteur, through a series of complicated experiments, was able to demonstrate not only that the air contained micro-organisms but also that these organisms were alive. He, and another great investigator, Robert Koch, were the first to demonstrate that these micro-organisms were capable of causing disease. The works of these two men dealt a death blow to superstí-

tious beliefs in such things as demons, and opened up the field of germ origin of disease, probably the most important movement in modern medicine.

In this part of the article we have very sketchily traced the history of various theories of causation of disease and various therapeutic approaches. Having established the theory of natural causation of disease, and the role of chemotherapy in treatment, let us now turn to an in depth study of the history of some of our modern chemotherapeutic agents.

PART II

Today the theory of natural causation of disease is universally accepted. Therapeutic regimens include diet, activity, and drugs. The last gained in importance in recent years with the ever increasing number of therapeutic agents being put on the market. But what drugs are most important? In an informal survey, 30 physicians, both specialists and general practitioners, were asked to name the five most important drugs in their medical practice.

A "drug," for the purposes of this article, was defined as any substance used to produce beneficial effects in the treatment of disease – either in the form of a cure or by alleviating symptoms. A second stipulation was that it be an exogenous substance: "Important" was here taken to mean providing the greatest relief to the greatest number of persons.

The drugs chosen are listed in Table I. Only one drug received the unanimous vote of all physicians – an antibiotic. Twenty-five of the thirty chose one of the penicillins. While there may seem to be some major omissions it must be remembered that the second part of the definition rules out many important therapeutic agents – e.g. catecholamines, steroids, etc.

TABLE I

Antibiotic (Penicillin)	30
Aspirin	28
Digitalis	25
Tranquilizer (Valium)	20
Diuretic (Thiazide)	18

Penicillin

Probably the greatest contribution made to the science of medical treatment in the twentieth century is the development of antibiotics. Those of us who have lived most of our lives in the age of antibiotics are often complacent in our approach to infection, unappreciative of the great advances that have occurred in this field of medicine in the last 30 years. A brief glimpse at the statistics in Table II will help drive home an appreciation of the magnitude of their importance, and the role that they have played in changing the practice of medicine.

Sir Alexander Fleming (1881 - 1955) is the man usually credited with the discovery of penicillin. One of the ironies of the discovery of penicillin by Fleming was that it was not really a discovery at all, but a recognition. Many people noted that their bacterial cultures, obtained with difficulty, and purified with painstaking care, were frequently ruined by the overgrowth of a mold which destroyed all or part of the colonies on the plate or in a broth. Hitherto these cultures had been discarded. These disconcerting events were reported as early as 1877 by Pasteur and Joubert, who even suggested that sometime it might be worthwhile therapeutically to look into the phenomenon. By 1885 the suggestion was made that one organism could block the growth of a second by secretion of a toxic substance. However, since most of these toxic substances were also toxic to test animals, there was relatively little interest in them.

The work of Fleming provided the major breakthrough in the development of antibiotics because he accepted the evidence for inhibition of staphylococcal growth following contamination of cultures with molds as an indication of production of a substance by the molds that was inhibitory for bacterial growth. He named the substance or substances in the filtrate "penicillin" and showed that it was not specifically inhibitory for staphylococci, but also inhibited the growth of many other gram positive organisms. Although Fleming attempted to make clinical use of his substance in the therapy of local infections he did not achieve a therapeutic breakthrough. Interest in Fleming's findings was virtually non-existent, so taken up were microbiologists with the new sulphonamides.

But the widespread use of the sulphonamides made the medical profession much more chemotherapeutically-oriented. In 1938, Florey and Chain once again took up the investigation of penicillin and produced a purified product. More experiments on animals showed that hemolytic streptococcal infections in mice were arrested. Extensive experimentation showed that penicillin was probably the most effective chemotherapeutic drug known, and moreover, was relatively non-toxic.

No-one can even guess at the number of lives that have been saved as the result of Fleming's astute observations, but it is safe to say that penicillin and the many new antibiotics subsequently developed, have played a major role in the sharp decline in the death rate over the past 30 years.

Aspirin

The second most commonly named drug was aspirin. Its wide use as an analgesic, antiinflammatory and antipyretic agent relieves more of the common "aches and pains" than any other drug. Because salicylic acid is found in several sources in nature there are several lines of descent listed in various phamacopoeias.

TABLE II

Cause of Death	Death Rate per 100,000	Per cent of Deaths – All Causes
1900:		
All Causes	1,719	100
1. *Pneumonia and influenza*	202	11.8
2. *Tuberculosis*	194	11.3
3. *Diarrhea and enteritis*	143	8.3
4. Heart diseases	137	8.0
5. Cerebral Vascular lesions	107	6.2
6. *Chronic nephritis*	81	4.7
7. Accidents	72	4.2
8. Cancer	64	3.7
*9. Certain diseases, early infancy	63	3.6
10. *Diphtheria*	40	2.3
1954:		
All Causes	919	100
1. Heart disease	347	37.9
2. Malignant neoplasms	146	15.8
3. Cerebral vascular lesions	104	11.3
4. Accidents	56	6.1
*5. Certain diseases, early infancy	39	4.3
6. *Pneumonia and influenza*	25	2.8
7. General arteriosclerosis	19	2.1
8. Diabetes mellitus	16	1.7
9. Congenital Malformations	13	1.4
10. Chronic and unspecified renal disorders	11	1.1

* Birth injuries, asphyxia, infections of newborn.

One description of aspirin appeared in 1763 in a paper presented to the Royal Society of London by one Edward Stone, a clergyman. Entitled "An Account of the Success of the Bark of the Willow in the Cure of Agues" it recommended a preparation containing white willow bark for treating "aguish and intermittent disorders" – the disease we now call malaria. The concoction relieved the feverish symptoms of malaria because it contained the antipyretic agent salicylic acid. The active ingredient was isolated more than 60 years after Stone's documentation by a Frenchman named Leroux. A compound of glucose and salicyl alcohol, it was given the name "salicin." Pure salicylic acid was derived from three different sources within a seven-year period 1835-42. Meadowsweet flowers, oil of wintergreen and Leroux's salicin were all found to contain salicylic acid.

The first synthetic salicylic acid was produced in 1852 by H. Gerland, and by the end of the decade the substance was being produced in sufficient quantity for therapeutic use.

In 1874 a Scot named T. J. MacLagan conducted an historic experiment with salicin. He was concerned with a patient who was suffering from "acute rheumatism" (rheumatic fever). Before administering the salicin to his patient, he himself took the drug in increasing dosage until he was assured there would be no untoward reactions. His patient responded almost immediately – as MacLagan himself wrote "The results exceeded my most sanguine expectations".

With increasing wider distribution, the drug was tried in more conditions with good results. Chronic rheumatoid arthritis and gout both responded to its action, as did non-rheumatic pains such as neuralgia and headache.

While salicylic acid was considered a "miracle drug" during its first years of use, it had devastating effects on the GI mucosa. Crude aspirin tablets, which disintegrated slowly and unevenly in the stomach, produced gastric ulceration and GI hemorrhage. This complication was first overcome by producing sodium salicylate, a less irritating compound, but nauseatingly sweet.

The real answer to this problem of toxicity was introduced by Charles Frédéric Gerhardt of Strasbourg, who in 1853 added an acetyl group to the basic salicylic acid. However his process was too long and too complicated for wide use. The acetylated compound was not mass produced until a chemist working for the German firm of Bayer discovered a simpler method of production. The Bayer product was called Aspirin – the "a" for the acetyl group, "spir" from the botanical name of the meadowsweet – Spiraea ulnaris. From that time on the Bayer trade-name Aspirin has been synonymous with acetylsalicylic acid.

Since the production of the acetylated compound in the late 1900's, "aspirin" has gone on to be the most widely used drug in the world. In 1962, for example, 27.2 million pounds of aspirin were produced in the U.S. alone. This represents 15 billion tablets. Many modifications and combinations have been synthesized but the basic ingredient still remains the substance of Stone's white willow bark.

DIGITALIS

"This medicine has restored (where the patient has been past all cure) beyond all Expectation . . . It opens the Breast and Lungs, frees them from Phlegm, cleanses the Ulcer . . . Persons in deep consumption, and given over by all Physicians, have been strangely recovered as to grow fat again."

— William Salmon, an English Physician

There is some question as to who was the first person to record the medicinal properties of the foxglove. In 1542 Leonard Fuchs compiled a herbal, "De historis stirpium", in which he introduced the Latin term Digitalis purpurea. In this book he describes digitalis as a purgative and an emetic. It is questionable that he recognized the drug's role in the treatment of dropsy. He was perhaps referring to this use when he wrote: "This plant is usually very effective in its action to thin, to dry up, to purge, and to free obstructions."

Throughout the 16th century the drug gained wider use, and with its inclusion in more herbals it was ascribed more powers. It first made its appearance in the prestigious London Pharmacopoeia in 1661, where it was recommended for epilepsy and as a sedative. Another major use was for consumption, which often times physicians had trouble differentiating from heart failure, since both involved the lungs. Thus digitalis was being used to treat many diseases it could not alleviate.

While there were a few astute men who used the drug sparingly and in small dosage, most used the drug indiscriminately. Digitalis thus gained a reputation for toxicity, and, its harmful effects outweighing the beneficial, it was stricken from the Pharmacopoeia in 1745.

The man who took up the cause of digitalis and had it reinstated as an important medicine was William Withering. In 1776, in a book describing all the plants of England, he wrote of the foxglove: "A dram of it taken internally excites violent vomiting. It is certainly a very active medicine and merits more attention than modern practice bestows upon it."

Withering's work, "Account of the Foxglove and Some of its Medical Uses: with Practical Remarks on Dropsy and Other Diseases", is a model of scientific reporting which re-established digitalis as one of the major drugs in medicine. Withering's interest was first centred on digitalis when his opinion was asked "concerning a family receipt for the cure of dropsy . . . kept a secret by an old woman in Shropshire." Foxglove, recognized as the active component in the mixture, was presumed to encourage the excretion of excess fluid. It is interesting to note that Withering continued to think of diuresis as its chief effect and to regard dropsy as the disease against which digitalis primarily acts, rather than on the weak heart responsible for it. In the conclusion of his Account he mentions the heart, stating that digitalis "has a power over the motion of the heart, to a degree yet unobserved in any other medicine, and that this power may be converted to salutary ends." The context indicates, however, that he believed the effect on the heart to be secondary to the loss of fluid.

While the results of Withering's investigations are admirable in the light of our present knowledge, modern investigators would be critical of his experimental techniques. Having suggested that comparative studies on the action of digitalis and other diuretics could be carried out on both higher animals and humans, he disregarded the animal experiments and proceeded directly to his experiments with human patients. In his study, Withering placed 158 patients on digitalis, varying the preparation and the dose administered. Of these, 101 showed some relief of symptoms. Of the remaining 57 patients many suffered from diseases not amenable to digitalis, e.g. consumption. Withering's conclusion included the following:

a) Of the available preparations, dried and powdered foxglove leaves produced the most benefit with fewest side effects.

b) There was an optimum quantity of the drug which could be administered as a single dose (in fact the amount he prescribed had only slightly less activity than the standardized tablet used in modern practice).

These findings gained for Withering great renown, and his Account brought him a fellowship in the Royal Society of London. He died in 1799 of consumption, a disease which he and many of his colleagues treated with digitalis.

In the years between Withering's Account and the present, much progress has been made in eliciting the physiological action of the drug, both its site and mode of action. New preparations have been produced, some more suited to certain cases than others.

Many other therapeutic agents have fascinating histories as well. Without the dedicated efforts of that vast army of biochemists and pharmacologists who continually strive to discover new drugs, and improve existing agents, medicine could not have made the great strides of the last century. With continued research and experimentation more diseases will undoubtedly become curable in the next century.

What will medical historians in the next century write concerning medicine in the 1960's and '70's? Will many of our therapeutic regimens become regarded as useless, thrown out, and replaced by new techniques? Undoubtedly they will. But which ones will these be?

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Student Research

Differences (?) In The Problems Of Medical Education Today And 129 Years Ago

Recently, there has occurred much discussion and re-evaluation of medical education, both in its method of teaching and in its method of examination. Many arguments have been raised against the continuation of written examinations, especially with regard to the type of medical knowledge they actually measure. The reasons are multiple and it is not the intention of this article to expand on them.

Many believe that the abolition of examinations represents a trend to a new, and, hopefully, a better type of educational system. However, in actuality abolition of examinations would return medical education to the period prior to 1840!

During this time, there was great pressure to introduce compulsory written examinations in order to improve the quality of medical students graduating. The arguments raised do not differ essentially from the problems medical education faces to-day — 129 years later.

Indeed, many of the points brought out in an article from the London Medical Gazette[1,2] of 1840-41 are just as relevant to-day, and should make one stop to consider what changes in medical education are actually needed if we are not merely to go full circle.

A typical examination of the day is as follows, from the University of London, 1841: (questions are excerpts from a much larger paper).

ANATOMY & PHYSIOLOGY:

1. Describe the form, situation, connexions, and structure of the pancreas, and state generally the nature of its secretions.

2. Describe the structure of the bronchial tubes and lungs. Do these structures take any, and if any what, share in the production of the respiratory movement? Enumerate the respiratory nerves, mention the muscles to which they are severally distributed, and the effects on the respiratory movements of injuries, whether accidental or experimental, of different parts of the cerebro-spinal axis.

3. Describe the intimate structure of a nerve, a plexus, and a ganglion.

CHEMISTRY:

1. What is the origin of force in the Voltaic battery? How is it accomplished?

2. State the general views which may be taken of the constitution of salts.

PHARMACY:

1. What is the most expeditious mode of preparing Hydrated Sesquioxide of Iron for exhibition in cases of poisoning by Arsenious acid? What reaction takes place when the former is mixed with a solution of the latter substance?

The following are excerpts from the editorial published in 1841. At the time of its writing, examinations were voluntary, and involved competitions for various prizes and medals.

"The return of the time for the examinations in the several medical schools reminds us of the necessity of again urging that they should be made to serve those purposes in medical education for which they are so evidently well adapted . . . At present many think it is better to be safe against having a low place than to take their chance of getting a high one . . . If the examinations were universal this would cease, and there could be no safety from a low and somewhat disreputable position except by the steady pursuit of knowledge . . ." and this would raise "the average standard of acquirement among the pupils . . ."

"School examinations, if all the students were compelled to pass them, might be made to remedy a great number of the defects which now confessedly exist in the scheme of medical education. For what purpose, for example, is all the difficult and tedious system of registration adopted? Registration of lectures entered to, and of lectures professedly attended, and of residence in London, and so forth. It is said, to insure that the student regularly and diligently pursues a proper course of studies. And all this would be very well if the system accomplished any fair proportion of what it pretends to; but it is notorious that all that the most scrupulous registration can determine is, that the student entered at a certain time upon the right to attend certain lectures, and that, at certain subsequent periods, he was residing in London; but whether he attended his lectures regularly or not is always a matter of doubt; and whehter he learnt anything from them — whether he slept through them, or listened attentively and studied them at home — is never enquired into, although it is obvious that this is the only question the answer to which would be really important. Now the whole system of registration might be safely dispensed with if at fixed times during the course of their studies all the medical pupils were made to pass examinations in these several subjects on which they had attended lectures

and if, not satisfactory, were stayed in their course and held back to learn the necessary elements . . . before they proceeded (as they now often do, unprepared and unfitly) to the study of its higher branches."

The greatest and hitherto the most insuperable evil which has resisted the benefits of every scheme of medical education is, that some of the students, after spending the greatest part of their time for their own amusement, and learning therein absolutely nothing of their profession, have yet been able to pass the ordeal of their examinations by a few months artificial and comparatively useless study. The system of grinding has undoubtedly attained in these times a degree of perfection as far as we know, in no other studies than those of Medicine, it ever even aspired to; and it now almost defies examination to detect the superficiality and inutility of the knowledge which it gives for the day of trial, but which vanished in the following month, and leaves the intellect as dull and empty as it was before the system was commenced. We do not say that the necessity of passing would altogether put an end to this baneful system; but we are certain that it would be to it both a heavy blow and a great discouragement . . . For at least, they would compel the student to be capable of passing examinations several times instead of once in the course of his study, and would give him by so many times a better chance of learning something of his profession, even in spite of himself.

Another evil that would be remedied by this measure is that to which we lately alluded as rendering desirable a system of more intimate personal instruction of the pupil.[1] If the life of a medical student may be well described by the word desultory, there is certainly no part of his life to which that term is more completely applicable than it is to the mode in which he commonly pursues his studies. He receives no more advice or guidance as to what books or even what subjects he should work at, than he does as to what rooms or what associates he should choose; nor is his own judgment in the matter more likely to lead him aright in one than in the other case. The only plan, if it deserves the name, that is set before him, is the curriculum of education required by the Apothecaries' Company; and this he cannot attempt to follow without absolute mischief. The subjects which it gives him to study at once and all together are so numerous and so wide, that not even the most resolutely industrious, though he may possess more than the average amount of abilities, can hope to master them all . . . The result of such a requirement is, that either all the subjects are totally neglected, or, which is not better, they are all studied but no one of them learned to any profitable degree. They are rare exceptions in which a student has the discernment to find out that he is misguided by the curriculum and must altogether neglect the majority of the subjects set before him for the sake of studying profitably some one or two of them. (Witness ELECTIVES!)

And even when such a subject of study is determined on, as with proper management might be learned well in the given period, still, for want of due guidance, every student throws away much, both of time and of labour . . . and after having worked, it may be hard and with much well-meant industry, he finds himself, when his examinations come, lamentably deficient; his labour expended at wrong times and in wrong directions, has been expended to no profit, and he is intellectually no better than the idler. "Frequent examination would be most beneficial."[1] "This is no imaginery picture . . . and the evil is the necessary and unavoidable result of the present systemless schemes of medical teaching[2]." "It is the result of the absurd mode in which the curriculum of education is arranged[1]."

Thus we see that the problems have indeed a familiar ring, but what about alternatives. Again the above article gives the answer, "What is wanted is, that each student should have at all times his work definitely apportioned to him, and should be instructed in the best mode of learning it . . . In a word, every student should be not merely lectured to, but tutorized; the personal instruction which, concentrated in the form of short grinding before examination, is now mischievous, should be made useful by being distributed over the whole period of study, and by being made the guide of all the student's progress."[2] (Witness Systems Teaching and In-Course Evaluation!)

HAVE WE NOT INDEED COME FULL CIRCLE!

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A History Of Immunology

Harvey Grosman, TTG

The germ of immunology grew out of the common knowledge that those who survived an infectious illness seldom contracted that disease again during their lifetime. Thucydides recorded that those who had survived the plague in Athens were able to nurse other plague sufferers without fear of re-infection. There are accounts of Mithridates, King of Pontus, protecting himself against poisons by drinking the blood of ducks treated with them, and also of Pliny the Elder, who regarded the livers of mad dogs as a cure for rabies. In 1733 Voltaire described an old Chinese custom, practised since the 15th century, of prophylactic inhalations of dried powders of smallpox crusts. The Turks, in turn, derived the custom which they called 'ingrafting', from the inhabitants of Circassia who used it to prevent the smallpox from disfiguring their beautiful daughters – an important source of revenue, since they were sold into harems which were prevalent at the time.

In 1721, Lady Mary Wortley Montagu, the wife of the British ambassador to Turkey, brought this custom of 'ingrafting' back to England.[1] The practice of inoculating people with smallpox virus obtained from the vesicles of mild cases of that disease became known as variolization, and thus began the history of immunization as we know it to-day. Although a desperate and hazardous undertaking, it proved better (2-3% mortaity) than suffering a disease which, in Voltaire's time, was affecting 'three score persons in every 100, of which 20 die and many more are disfigured for life.'[2]

The practice of variolization rapidly spread throughout the world, although it was given a mixed reception in many countries, America being one. It is of interest that, in 1766, the American colonial troops under Gen. Washington were unable to capture Quebec apparently because smallpox was prevalent amongst them, and only one-half of the army was fit for duty. In contrast, the much smaller British army, who were well variolated, were able to hold out until re-inforcements arrived. Ten years later, in 1776, Washington ordered his entire army to be inoculated, but by that time the whole course of history had been affected and Canada had been preserved for the British Empire![8]

THE FIRST VACCINATION – 1774

Benjamin Jesty, familiar with the popular belief among farmer-folk that an attack of the relatively trivial cowpox, or vaccinia (vacca, a cow), in humans afforded immunity to smallpox, and even to variolization itself, scratched the arms of his wife and two sons with a 'stocking needle' and inserted vaccinia virus obtained from the lesions on the udders of cows affected with the disease. Benjamin was reproached by the inhabitants of Dorset as an 'inhuman brute' for daring to perform experiments on his own family; however, despite being frequently exposed to smallpox over the following years, no one in the family took the disease.[1]

However, variolization did not become a regular practice until Edward Jenner (1749-1823), a physician from Berkeley, Gloucestershire, became the first person to methodically and scientifically confirm a milk-maid's assertion: 'I cannot take the smallpox for I have had cowpox'. In 1796 Jenner inoculated James Phipps, a healthy 8-year-old boy, with matter from a typical cowpox lesion on the hand of a dairy-maid, Sarah Nelmes, who had been accidentally infected by a cow. Inoculation of the boy with smallpox matter about 6 months later and again in several months was unsuccessful. In 1798, at his own expense, Jenner published his classic 'An Inquiry into the Causes and Effects of the Variolae Vaccinia, a disease discovered in some of the Western Counties of England, particularly Gloucestershire and known by the name of the Cowpox.'[4 9]

In the early years, criticism, often bitter and unrelenting, came from various quarters, both professional and lay. Apart from those physicians who were sceptical or had vested interests in variolization, there were many clergy who believed that the practice of vaccination must be sacrilegious, since it was directed against an act of God (smallpox). Surprisingly also, a surgeon named John Birch objected to vaccination only because it was too effective against smallpox, 'an important method of decreasing the population particularly in large and poor families.'[10]

Variolization, which had been known to be dangerous both to the individual and the community for a period of over 50 years, was at last made illegal by the First Vaccination Act of 1840, 17 years after Jenner's death. Deaths due to smallpox in the 8th century had averaged 3,000-4,000/million pop. and in the period 1847-1853 it was reduced to 305/million pop. By 1900, the British national death rate due to smallpox was 13/million population – quite a change![5]

CONTRIBUTIONS OF LOUIS PASTEUR (1822-1895)

Although in the middle of the 19th century comparatively little was understood of the ways in which bacteria could cause harm in the body, Pasteur proceeded to develop valid methods for immunization. Pasteur found that when a culture of chicken cholera bacillus, which by accident had been left on a bench over a summer vacation, was injected into chickens, no disease was produced; and indeed, when these same chickens were injected with a fresh culture of highly virulent cholera bacilli, they also did not become ill. In short, they had been immunized with the first successfully live, attenu-

ated culture of bacteria.[4] In honour of Jenner, Pasteur called his new treatment 'vaccination', a term which has been used subsequently for injection (or ingestion of) bacteria, viruses, their products, and even pollen materials, as a method of deriving future immunity against disease.

Working next on anthrax, Pasteur found that anthrax bacilli in broth cultures kept at 42-43°C. lost their virulence i.e. were attenuated, at a rate proportional to the duration of cultivation. In 1881, Pasteur and his coworkers, Cumberland and Roux, carried out their famous trial of anthrax vaccine at Pouilly-le-Fort in which all the vaccinated animals lived, except one which died of unrelated causes, and all the unvaccinated died.[11]

At age 59, although crippled as the result of a stroke, Pasteur began research on the disease rabies. He found that he could attenuate the etiological agent (a virus / a poison) by drying in air the spinal cord of rabbits infected with the disease.[12] In 1885, when Joseph Meister, a 9-year-old boy, was bitten 14 times by a rabid dog, he was sent by his physician on the third day of his bites to Pasteur to receive his vaccine. Remarkably, the boy survived and later grew up to become the gatekeeper of the Pasteur Institute. In 1940 he committed suicide so as not to open to the Germans the crypt in the Institute where Pasteur was buried[1,4]

In 1886, Salmon and Theobald Smith found that even heat-killed bacilli, when injected, retained their antigenicity and could induce an active immunity without the danger of a return of virulence that might accompany attenuated strains.

THE "ADVENT" OF ANTIBODIES

In 1888, Roux and Yersin (at Pasteur Institute, Paris) discovered that a bacterium-free filtrate of a culture of the diphtheria bacillus contained the 'exotoxin' of that organism. In 1890, von Behring and Kitasato (at Koch's Institute in Berlin) were able to demonstrate the formation of specific neutralizing substances to tetanus, and later to diphtheria toxins, in tetanus and diphtheria-immune animals, and that this immunity could be transferred passively by giving non-immune animals serum containing these 'anti-toxins'.[13] The German chemist, Paul Ehrlich, demonstrated that toxins other than those of bacterial origin could also stimulate the body to manufacture specific antibodies. In 1894, Roux demonstrated that not only could immunity to tetanus and diphtheria be passively transferred, but also that, if given early enough, could cure an infected, previously non-immunized person.

Next came investigations into the nature of antibodies, and anti-toxin – toxin reactions. In 1893, Buchner noticed that fresh 'immune' serum, heated to 56°C., lost its bactericidal properties and he called this heat-labile constituent, which contributed in some way to the immunological process, ALEXINE (known to-day as COMPLEMENT). In 1894, Richard Pfeiffer described the ability of antibodies against cholera to disintegrate and dissolve bacilli (bacterolysins); and Bordet, in 1895, showed that in cholera antibody-antigen reactions, there existed a heat-stable element, probably antibody, and a heat-labile factor which was also found in normal serum (alexine). In 1889, Charriu and Roger found that when the gut organism, *Pseudomonas pyocyanea*, was grown in the presence of an animal injected with that organism, its growth took place in a lumpy manner. The clinical application of this agglutination reaction to the diagnosis of enteric fever was made by Widal in 1896. In 1897, Kraus showed that a clear filtrate of a bacterial culture could often induce, after injection into a suitable animal, an antibody (a precipitin) which formed a precipitate when added to the filtrate used for injection.

The outstanding characteristic of an antibody is its specificity. As immunologists became aware of the exquisite selectivity of such a tool, they were soon exploiting it for an analysis of the antigenic make-up of bacteria and other antigenic complexes. In 1900, the specificity of antibodies was studied by Landsteiner who discovered the A, B, O blood groups on red blood cells and specific naturally-occurring iso-antibodies to them. Nuttal's research into the cross-reactivity of certain antibodies revealed that monkeys were a more closely related species to man than were the lower apes. In the 1930's and 1940's, similar immunological methods were used by many to classify many bacteria; for example, such people as Neufeld, Heidelberger, and Avery who worked on the classification of pneumococci so that appropriate, comprehensive anti-pneumococcal vaccines could be manufactured to combat pneumococcal infections during the period before the widespread use of antibiotics. Antibacterial sera or vaccines were the only modes of specific chemotherapy for such infections as gas gangrene, plague, brucellosis, anthrax, scarlet fever, and typhoid until the glorious age of antibiotics with the introduction of sulfonamides in 1936 and penicillin in 1941.

THE CELLULAR (1884) VERSUS THE HUMORAL (1888) THEORY OF IMMUNITY

The cellular theory of immunity was predominantly the work of Elie Ilya Ilyich Metchnikoff (1845-1916), a Russian zoologist who gave the name "phagocytes" (Greek: phagein to eat; kutos - cell) to certain body cells which ingested and destroyed invading microorganisms, whether alive or dead, and other minute foreign particles. The phagocytes, which were numerous in the spleen, lymphatic glands, bone marrow, and liver were termed either 'wandering' or 'fixed'. The microorganisms in acute infections were mainly the concern of the wandering polymorphonuclear leucocytes, normally found chiefly in the blood stream, which Metchnikoff named 'microphages'. Metchnikoff failed to appreciate,

however, that these cells, when deprived of the assistance of the plasma, were incapable of ingesting bacteria and other particles. It is the changes in the plasma and serum of the body with which immunity is largely concerned.

The humoral theory was introduced by George Nuttal (1862-1937) of Cambridge, who was working at that time in Göttingen, on the bactericidal action of blood. According to him, the action of Metchnikoff's phagocytic cells was merely that of scavenging — a mechanism for removing bacteria, after these had been devitalized by 'humoral' influences present in blood.

These two theories divided scientists for a short time, but with the work of Pfeiffer on the presence of bacteriolysins in blood in response to cholera infection, and the work of von Behring and Kitasato and their discovery of anti-toxins against diphtheria and tetanus, the 'humoral' theory became more favoured. In 1903, Almroth Wright effected his own reconciliation of these theories by proposing that the main action of the increased amounts of specific antibody after infection was to reinforce the destructive action of the phagocytes. He called this property, acquired by the blood, 'opsonic' from the Greek 'opsono' — 'I prepare food for . . .', and the substance itself 'opsonin.' He also developed an 'in vitro' diagnostic and prognostic test – the opsonic index, which measured the phagocytic processes present in patients' blood during different illnesses. Almroth found, too, that some antiseptics were ineffectual, and indeed, even harmful if they killed leucocytes along with the bacteria.[22]

THE FATHER OF IMMUNOCHEMISTRY — PAUL EHRLICH

In the early years of this century, several investigators turned their interest to the fundamental aspects of the manner in which an antibody interacted with its homologous antigen. Hans Buchner (1893) demonstrated that tetanus toxin-antitoxin mixture, while non-toxic for mice, was toxic to guinea pigs, thus proving that toxin was simply destroyed by anti-toxin as was previously thought.

The next important contribution to this problem was made by Paul Ehrlich (1854-1915), who may be regarded as the pioneer of immunochemistry, since he was the first to introduce exact quantitative measurements as being the best solution to this problem. Ehrlich conceived antibody-antigen union to be similar to that between a strong acid and a strong base, and in this way he accounted for the varying proportions in which antibody and antigen combine. He also developed the fundamental notion that a toxin has two distinct and separate properties associated with two distinct reactive areas; that is, its ability to combine with anti-toxin (the 'haptophore' part), and its lethal or toxic properties (the 'toxophore' part). Ehrlich's other contributions included being the first to point out the important differences between passive and active immunization, and his 'side chain' or 'receptor' theory, published in 1897, concerning the mechanism of antibody production. This work had a profound influence in stimulating further fundamental study in these areas.[14]

In 1903, Bordet considered that serological reactions were akin to adsorptive phenomena and were not in the class of chemical interactions as Ehrlich had envisioned. In the same year, the chemists Arrhenius and Madsen, maintained that the curve of neutralization of toxin and antitoxin is similar to that in which a weak acid is neutralized by a weak base. Fortuitously, predictions made from this latter theory have been borne out in practice.

OTHER ASPECTS OF THE IMMUNOLOGICAL RESPONSE

The widely held teleologcal view that antibody productions was designed specifically to protect the infected host, received a blow when it was observed that sometimes the access of antigen to a previously exposed host resulted in severe symptoms and even death. This phenomenon, in which an immunological response leads to reactions damaging to the cells of the body is referred to as *hypersensitivity*. The original data, on which this idea is based, were provided by Portier and Richet (1902). They termed this development of sensitivity to relatively harmless substances, *anaphylaxis,* in contrast to prophylaxis.[15]

In 1903, Maurice Arthus described local anaphylaxis induced by daily subcutaneous injections of horse serum into rabbits, producing a local lesion which progressed from local oedema and inflammation to an area of frank necrosis.[16]

In 1905, von Pirquet and Schick showed that repeated use of serum in the same individual was not only attended by grave risk of anaphylactic reactions, but also led to increasingly severe attacks of a delayed complex of symptoms known as 'serum sickness'.[17]

What were the mechanisms underlying anaphylaxis? A 'humoral' theory was proposed that when antigen and antibody reacted together in plasma, they activated a latent proteolytic enzyme which split off highly toxic fragments from the antigen producing the symptoms of anaphylaxis. In 1910, Sir Henry H. Dale showed that histamine injections could mimic many, though not quite all, of the effects of anaphylaxis.[10] Histamine was present in blood and tissue cells, but not in plasma, and the interaction of antigen with sessile antibody of the cells, damaging these cells with resultant histamine release and perhaps other manifestations, seemed to provide a satisfactory solution. Current knowledge has shown that both 'humoral' and 'cellular' notions are valid in different contexts.

IMMUNOPATHOLOGY

Once having recognized that the immunological response was not only evoked by toxins but also by many bland foreign substances, and that the reintroduction of

the antigen could produce a harmful reaction in a sensitized animal, it was natural to seek an explanation for some diseases where the role of infective agents was not obvious, in terms of the untoward consequences of responses, which under other circumstances might be harmless or useful. For example, it had been recognized since Blackley's monograph on 'The Causes and Nature of Hay Fever' written in 1873, that pollen was closely associated with hay fever and asthma, but how this association came about was quite obscure.

In 1911, Noon in America and Freeman in Britain, followed by Cooke, who, between 1916 and 1933, made an extensive study of skin sensitivity, clearly showed that these diseases were often associated with an anaphylactic type of sensitivity to pollen extracts. Following an early observation that sensitized animals could be made temporarily resistant to anaphylaxis by cautious administration of large doses of antigen by subcutaneous injection, Freeman began the practice of desensitization which was greatly extended by Cooke. Other workers, particularly many German pathologists in the 1920's, were much impressed by the similarity between the histological appearance of lesions produced by reinjection of antigen into sensitized animals – which they recognized as a form of inflammatory response and named 'allergische hyperergische Endzüdung' – and those seen in rheumatic fever. When the Japanese pathologist Masugi in 1934 injected antiserum prepared in ducks against rabbit kidney tissue back into rabbits, and produced an acute glomerulonephritis, which was the first acceptable experimental imitation of the human disease, interest in a possible immunological etiology was kindled.

AUTO-IMMUNITY

Ehrlich's phrase 'horror autotoxicus' implied that the body would not react against its own constituents. However, this principle was shaken by the work of Witebsky who showed that some body tissues (eg. eye lens, pancreas, thyroid, and brain) contained antigenic material specific to these tissues; and by the work of Coombs, Mourant and Race who introduced the antiglobulin test in 1945; and by Boorman, Loutit and Dodd, who in 1946, used this test to show that certain patients with acquired haemolytic anemia had antibodies against their own blood cells.

SUMMARY OF THE HISTORY OF IMMUNIZATION

Apart from vaccination against smallpox and the Pasteurian treatment for rabies, the first applications to human disease were passive serum treatment, first of diphtheria and later, during the first World War, of tetanus and gas gangrene. Active immunization against enteric disease was introduced for troops serving abroad in the early 1900's.

A great step forward was made when, in 1923, Glenny and Ramon independently discovered that careful formaldehyde treatment of several toxin preparations destroyed their toxic properties without diminishing their immunizing capacity. This 'toxoid' was much safer than previously used mixtures of toxin and horse antitoxin.[7] Glenny shortly afterwards found that adsorption of antigens onto alum (or various other adjuvants) often rendered them much more effective as immunizing agents, so that a more long-lasting response was obtained with fewer injections and with material. Prophylactic immunization against diphtheria on a mass scale became a practicable policy, and a fine example was set by the town of Hamilton, Ontario, which by 1933 succeeded in completely wiping out this disease from its population! Also, two Canadians, P. J. Moloney and C. J. Fraser, introduced an intradermal test in 1927, called the Moloney Test, to ascertain the susceptibility of a person to toxoid. A tetanus toxoid was developed about the same time, but was not tested on a large scale until W.W. II, when it was found to reduce the incidence of tetanus infection of wounds to an almost negligible proportion.

Many other immunizing agents were tested during the years betweeen the two world wars, in the form of killed bacteria and their products, killed virus-infected tissues, or living, attenuated strains. Some were apparently useless, such as those against streptococci and staphylococci, since prophylactic immunization was impossible when the number of antigenically distinct strains of the infective bacterium, virus, or rickettsia at large in a community was so great that they could not all be included in the prophylactic preparation, or when they did not all act by elaborating a single kind of exotoxin. However, some were very successful, such as the attenuated yellow fever vaccine developed around 1936. Interestingly, Yellow Jack or Yellow Fever, got its name, not from the jaundiced appearance of people stricken with it, but from the yellow quarantine flag used by shipping at that time to indicate the presence of the disease on board.[19]

Even after the advent of antibiotics, vaccines remain essential since purifying viruses, together with better understanding of their epidemiology, have rendered active immunization against several virus diseases safe, easy and effective; for example, vaccines for yellow fever, smallpox, rabies, typhus, poliomyelitis, and influenza, and in the future possible vaccines for adenovirus infections, and even the common cold. There is exciting news from the University of Glasgow, where Drs. Oswell and William Jarrett have isolated and cultured the feline (cat) leukemia virus (SeLV) in the embryonic cells of mice, and have, therefore, opened the possibility of producing a vaccine against this dreaded disease.[20]

At the same time, improved methods of culture and preservation of the important antigenic components of bacteria with a minimum of toxic factors, have led to the development of effective vaccines for pertussis, and plague, although those against such scourges as cholera and helminthic and protozoal diseases are still not satisfactory. Living bacterial vaccines, of which the

first to be used on a wide scale in man was BCG (the attenuated strain of tubercle bacilli named in 1906 Bacille Calmette-Guérin, after its originators, have also been developed; these include attenuated strains of *Brucella abortus* and *Brucella tularense.*

IMMUNO-HAEMATOLOGY

Immunology and haematology crossed paths early in their histories. With the discovery of the main blood groups, A, B, AB, and O by Landsteiner in 1901, the use of blood transfusion became commonplace after the introduction of anti-coagulant (sodium citrate) in 1915. In 1938, Levine implicated the Rhesus antigen (Rh factor) as the main relevant factor in haemolytic disease of the newborn. But since the very recent introduction of Rhogam which, when given to Rh negative mothers with Rh positive babies within 72 hours of parturition will prevent the sensitization of the mother in future pregnancies, the disease erythroblastosis foetalis will become a disease of the past. In 1945 Coombs, Mourant, and Race developed a technique for testing the presence of specific antibodies, such as the Rh antibodies, called the Indirect Coombs Test. In 1943 Cumley and Irwin showed the existence of definite antigenic differences between plasma proteins of different varieties of pigeons, and, in man, inherited antigenic differences have been found in the α, β and γ globulin groups.

The study of red blood cell transplants (blood transfusion) led to the study of tissue transplants. Medawar's extensive work on rabbits in 1944-1945 showed that rejection of tissue grafts, both hetero and homografts was due to immunization of the recipient by the donor's tissue. This led to work that eventually developed the concept of immunological tolerance. This field of study is of prime importance today with kidney and heart transplants being carried out on a regular basis. The solution, if found, will most probably be an immunological one.

MODERN IMMUNOCHEMISTRY

Heidelberger, Marrack, and colleagues from 1930 onwards studied the interaction of antigen and antibody by exact and sensitive quantitative methods which had been unavailable to earlier workers such as Ehrlich. They developed the 'Lattice' hypothesis explaining how interaction between two large molecules by means of specific and definite bonds could apparently lead to combination in variable proportions. By the use of quantitative micro-methods, it became possible to measure precipitating antibodies in serum accurately, and to predict how antigen-antibody interactions would behave in the test tube. In 1946, Elek, Oudin, and Ouchterlony devised the idea of using gel diffusion techniques to isolate and identify antigens and/or antibodies. In 1938, one year after Tiselius developed his technique of electrophoresis and the separation of serum proteins, Tiselius and Kabat showed that antibodies were γ-globulins. Combining the techniques of Tiselius and Ouchterlony, Grabar and Williams, in 1953, developed the technique of immuno-electrophoresis. In 1956, a protein, later to be called *Interferon,* was first observed and isolated from a chick-embryo tissue culture exposed to influenza virus, indicating that cells were capable of responding (immunologically?) to invasion by a virus.[21] The implications for the future use of Interferon against viral infections is still being worked on. In 1959, R. R. Porter used papain to split antibodies into two, Fab or antigen-binding portions, and one Fc or characterizing portion. Since then, the molecular structure of antibodies has been investigated with great success.

MODERN IMMUNOPATHOLOGY

Due largely to work by such people as Kunkel, Dixon, Weigle, and Isnizaka, many diseases that formerly seemed to be of unknown etiology, now appear to be related to an auto-immune mechanism. There is now a long and wide-ranging list of such diseases, including acquired haemolytic anemia, Hashimoto's thyroiditis, myasthenia gravis, ulcerative colitis, pemphigus, glomerulonephritis, systemic lupus, sympathetic ophthalmia, pernicious anemia, atrophic gastritis, autospermagglutinins, lupoid hepatitis, myocarditis, encephalitis, and rheumatoid arthritis[23,24]

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The Influence Of Social Experience On Men Of Science— A Historical Perspective

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To modern man, the very terms "science" and "scientist" engender images of smile-less, bespectacled men performing experiments and recording precise observations. It is no accident that this view of the scientist and what he does, has come to prevail in the public mind. Since the days of Hippocrates of Cos, perhaps one of the earliest men to be thought of as a scientist, careful observation has been the essence of the talent of the man whom today we call scientist.

But going beyond the how and what, the customary approach of students of the history of science, let us examine the why. Why, for instance, was Hippocrates drawn to medicine to the degree that he was in the first place? Why did Plato establish the Academy, and Aristotle the Lyceum, both of which institutions were to prove to be fertile grounds for enquiring minds, safe havens for students' instruction? What led Democritus in the 4th century B.C. to think about atomism and what led Lucretius in the 1st century B.C. to incorporate this atomism in his *DeRerum Natura?* Why did the medieval Arab Geber become interested in alchemy? Why did 16th century A.D. Vesalius take up the verification of the until then sacredly accepted anatomical gospel of 2nd century Galen? What led Aristotle to synthesize, Ptolemy to account for, Copernicus to re-examine, Galileo to invent, Newton to prove, Paracelsus to question, Lavoisier to define, Priestley to summarize, Dalton to theorize, Desagulier, Franklin and Cavendish to discover, Galvani and Volta to argue, in short, what influenced these men to follow the course of action they did?

One fact holds validity for all times; that is, that man is affected by his environment. According to this theory then, these men did what they did because their environment supplied them with social experiences that were conducive to their particular development.

With the invention of the alphabet in Phoenicia in 1200 B.C. literacy, and thus, control over data, was gained and marked an important threshold in the progress of science. The invention of mathematical writing met the need of antiquity for the accounting involved in hiring a slave, obtaining services, or tallying a king's shares. The flooding of the river Nile twice a year, advanced the development of astronomical observation mainly for the purpose of predicting the time of flood.

In Mesopotamia, building of canals led to the development of geometry. In Egypt, building of pyramids necessitated a mensuration system, while administering or managing the building personnel required the use of arithmetic.

The men of the 6th century B.C. who took an interest in what we consider today to be the sciences, men such as Thales of Miletus, Anaximander and Heroclitus, had a number of common factors in their background. They all made a fortune at commerce, travelled to Egypt and other parts of their world, retired to a life of study and community service, and were benefactors of their towns. Moreover, it is significant to note that they all converged on Miletus, a major sea port where shipping and dye industry prospered, where great social complexes existed, and where a river flowed inwards from the sea making fertile flood plains suitable for agriculture and sheep grazing. These men sought answers to the questions of their day: What is the world like; when do eclipses occur; what are things made of; is everything always changing or stationary? However, since conclusions were arrived at by the use of logic or reasoning, and not by experiment, our criteria of what is science are not satisfied. Nevertheless, these philosophers were the forerunners of modern scientists. It is interesting to note that after the Persian conquest of Ionia in 475 B.C., and the subsequent imposition of despotic rule, Ionian Science suffered a great decline. People moved and their ideas moved with them. Athens, a consolidated stable area, became the next centre of creative thought and expression.

An examination of the conditions of Aristotle's life provides clues as to his various fields of interest. After parting from Plato's Academy, Aristotle proceeded to Assos and Atarossos, two towns under the dictatorship of a former student friend of his. Here, under benevolent despotism, he researched the needs and ways of good government, with the view of providing better government for the community. This useful aim contrasts sharply with the former aim of science: self pleasure. All factors remaining the same, except the surrounding conditions, is it not natural to suggest that environment conditions the line of reasoning a man takes, the type of problem upon which he focuses his attention?

After Aristotle, Greek scientists, deprived by Alexander the Great of the hope of being appointed to the government, turned in a new direction. Science came to be cultivated for its own sake, to seek truth. This is evidenced by the development of mathematics by Pythagoras as the mirror of reality. From 300 B.C. on, the main aim of Greek science became the achievement of coherence within a framework, and not the honest accumulation of facts. Since the Romans controlled the trade areas and did not come to terms with the Greeks in intellectual fields, scientific thinking was neither nourished nor spread. The rise of mystery religions and their

influx from the Orient, the denial of reason by Pythagoreanism, and the wish of the despotic kings of city states to have their reputations enhanced by the work of scientists were added reasons for the decline of Greek Science.

Around 117 A.D., in the post Caesar era, Rome achieved its greatest fame and largest geographical area. With Jews and Christians attracted to Rome, and various cultures (Babylon, Britain) brought into contact, the foundations of the Roman Intellectual Revolution were laid. However, the advent of Christianity, with its emphasis on faith and de-emphasis on scientific reasoning, successfully prevented the immediate further development of science, save for the monumental work of the great medical man Claudius Galen. In spite of the singular advance of medicine, after this period Roman science is only a memory.

As the population of Rome became demoralized, as the standard of living decreased, and belief in magic or systematic hidden knowledge spread, the peripheral parts of Europe (France, Belgium) prospered. Manufacturing soon increased, the standard of living rose, and yet, but for the rapid advances of technology, scientific activity remained at a minimum. In no small measure the missionary work of the early Christian church is responsible for this. Preaching of the wonders of God, citing miracles as facts and turning to numerology, the attitude that science is useless, was fostered. Under these conditions only science fiction, not science, could flourish.

Around 734 A.D., when Alfred the Great ruled the British, King Canute the Danes, and Charlemagne the Western Europeans, there was a marked increase in scientific and pseudo-scientific activity. The Benedictine monk Bede, living in a northern English monastery, was an outstanding scholar. He wrote two books broadly dealing with science, and exhibited the method of data tabulation and conclusion extraction, the forerunner of the Scientific Method. With the important invention of the stirrup, armed riders came into existence, and long-distance overland communications improved. At this time, contact with the Arab world also occurred, facilitating the exchange of manuscripts. This rapid extention of new experiences and communication, resulted in the use of windmills certainly by 900 A.D., great interest in gem stones, and the revival of Pliny's "Natural History". In spite of the preoccupation with mechanization and devices, the emphasis exerted by the Church lay on development of literature. Thus work carried on in the scriptoria of monasteries. The principal active science was medicine, especially the branch related to animals.

At this period in history, the Arab world, governed by a theocracy, and following the Koran of L. Quasiam Mohammed, made tremendous advances in the field of science. The Baghdad area enjoyed the services of big Jewish and Christian hospitals, proximity to the University of Antioch, and the introduction of Chinese sugar — something of medicinal value. In addition, its Khalif, Al Amum, built libraries, employed translators for the purpose of transcribing Greek and Syrian scientific literature into Arabic, and encouraged discussions of scholars in his audience.

By 900 A.D. accumulated Arabic knowledge showed diversification and organization in many libraries under the headings:

1) Native Sciences (Koran study, literature, etc.)
2) Foreign Sciences (philosophy, geometry, alchemy, etc).

The use of Aristotelian logic was widespread and the development of the critical faculties was strongly encouraged in all places of learning. The updating of previously recorded astronomical data indicated the dissatisfaction of the Arabs with the accuracy of some earlier scientists.

The great contribution of the Arabs lay in using Nature to explain religious ideas and various social practices. Coupled with this form of scientific thinking, the adoption of Greek science made possible the great leap from more ancient forms of science to Western European science.

The beginning of modern science is found in medieval Europe. Men like Albertus Magnus, Thomas Aquinas and Roger Bacon began to advocate the use of experiment instead of reason to test validity. In England, particularly in the 13th century, science was flourishing. The Franciscans, with their headquarters at Oxford, spread the Theory of Proportions, and used it in developing new ideas in physics, especially mechanics. The new philosophy of Bacon contained in his *Opus Major* and *Opus Minor* laid claim to a new standard of truth; the truth of experiment and observation.

It is small wonder that England led the field in giving creative thought expression. The Magna Carta of 1215 had created a climate highly conducive to creative work. The establishment of feudalism, with the King as the central focus, caused major changes in the organization of all levels of society. The replacement of previously existing infinite variations with a uniformity implies the use of generalization, one of the fundamental techniques of modern science. Since records had to be kept, literacy became very important. Mathematics, as well, found a new function in running the state.

Once again, as during the building of pyramids in Egypt, it was the environment that caused a developmental change in science. With mathematics and markets, the science of weights developed. From weights flowed the idea of momentum, and momentum suggested acceleration. And so, a chain reaction was set off.

The development of alchemy provides a further insight. The role of religion in the development of alchemy

cannot be underestimated. As early Arabic and Christian alchemy were combined in Medieval Europe after 1100 A.D., both body and spirit were seen in metals. Gold was considered to be the purest form of ore, and it was thought that all things tended toward gold. The aim of alchemy was the speeding up of the process of transformation of base to noble substance. Fitting perhaps to this aim, baptizing in alchemy, meant dipping metal into a solution of salts changing thereby the blackness of the metal. Thus, a religious world developed a science that casted the natural world into religious copy. The equipment and methods developed at this time lasted until the 19th century.

The Scientific Revolution began with men like the German Paracelsus, the Pole Copernicus, and the Belgian Vesalius and Bauer. The work of all these men falls into the fertile period of 1473 to 1546. Paracelsus, who had an alchemical background, was active in attacking the medical practices of his day in Germany during the Reformation. As Luther bombarded the Diet of Worms with his "revolutionary" petition, Paracelsus hammered away with his idea that "new doctors should be men of heart, not silken gowns" and that for each disease there is an alchemical medicine. He thus established the experimental chemical basis of modern medicine.

The environment of Copernicus was conducive to the fostering of his inborn interest in the stars. Having much free time as a bishop's assistant, he spent it on his hobby. His being invited by the Pope to reform the calendar was a perfect opportunity to turn this hobby into purposeful research. The book, "Revolution of the Heavenly Bodies" containing his findings and his heliocentric theory, was not paid any attention for sixty years after its publication, simply because there was no one to take an interest in it. Not until Galileo, around 1600, picked up and lectured on the significance of Copernicus' findings, did the Church put the book on the Index, on which it remained until 1835. The comet of 1588 played a great part in sparking interest in astronomy, and the degree of this renewed interest is reflected in the important work of the astronomer Kepler, who worked in Germany without the hindrance of the Catholic Church, suffered by Galileo in Italy.

Vesalius came from a Belgian physician's family that had a great library. The intellectual experiences of his early life must have spurred him on to University studies, while the direction of his interests must have been influenced by the family's collection of great medical books, probably saturated with Galen. In the same year that Luther's argument with the Church reached a climax, and the works of Copernicus were published (1543), Vesalius performed dissections and prepared and published anatomical drawings. Many of these drawings were not in harmony with the centuries-long accepted ideas of Galen, and accordingly were widely criticized in some quarters, while praised in others.

George Bauer, or Agricola, was yet one more person trained as a doctor who applied his training in careful observation to his hobby: mining. In his attractively illustrated book, *De Re Metallica,* published in 1556, he expounded the opinion that close observation was required in fields of scientific endeavour.

An examination of the lives of all the aforementioned men reveals an interesting set of common characteristics. They were all University educated, first in their own country, then in Italy; they were all northern Europeans, not Italians; none of them was a theologian; they all studied medicine, and all pursued the work for which they were noted as hobbyists.

As is evidenced by the ancient and medieval cases cited, the environment played a crucially important part in what these "scientists" did, and when. It is clear also that the "why" of their doing was closely related to the social experiences to which they had been subjected.

The advent of modern science did not change the picture. The early scientific societies banded together men of similar backgrounds, social position and interest. Now, in the framework of a social club, rich men who had time on their hands, performed experiments and read each other's papers. They began to seek revelations in laboratories and this encouraged the design and manufacture of diverse instruments. Thus a new segment of the modern scientific team came into existence; the technicians and instrument makers. As more and more people attempted to satisfy their aroused curiosity about the heavens, or falling bodies, or alchemy, or mining, it became "the thing" to belong to a society and have one's paper published, thereby achieving the fringe benefits of fame and immortality.

As we have seen in the work of Aristotle at Assos, Galen in Rome, the Benedictine monk Bede in England, the hospitals of Baghdad, the University of Antioch, the writings of Roger Bacon, the alchemy of the Arab Jabir, the medicine of the German Paracelsus, the astronomy of the Pole Copernicus, the anatomy of the Belgian Vesalius, and the work of modern physicists and mathematicians, they all were influenced by the social experiences they underwent in the company of the people around them. With every new civilization science took on a new turn. Thus science was culturally conditioned, and therefore, by necessity, it had to exhibit the marks of the conditioning. This it did so completely that it created an artificial world within which it tried to become the organizing value for all experience. In the twentieth century it seems certainly to have completely succeeded.

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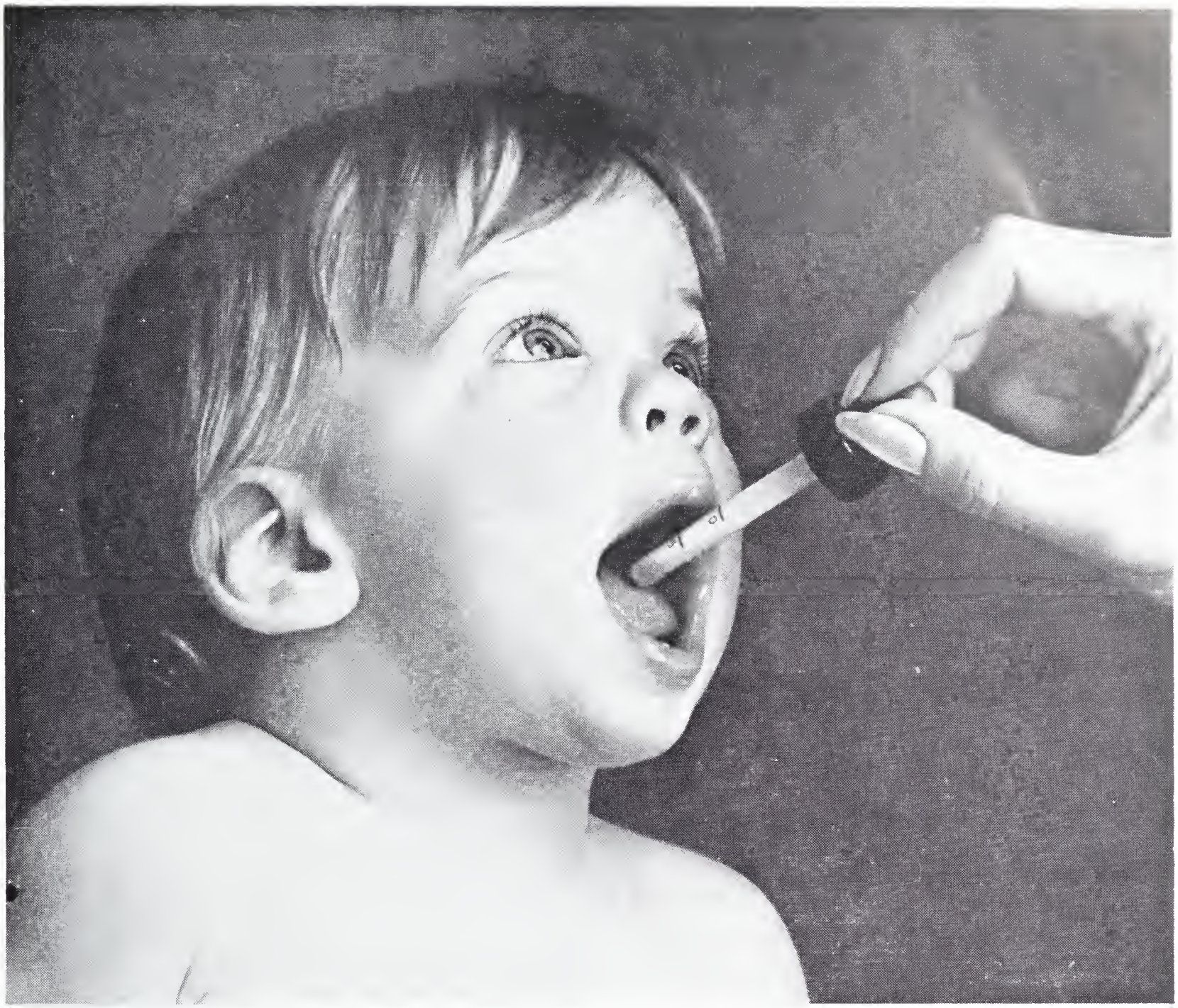

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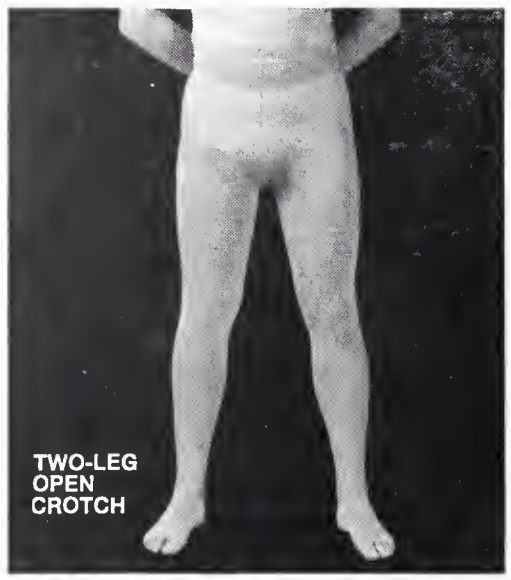
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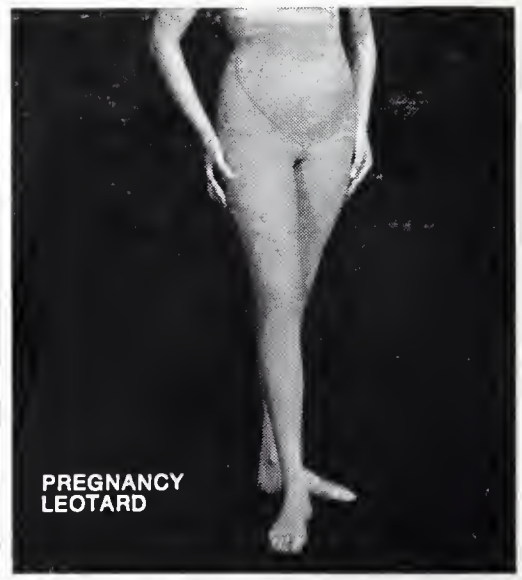
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